TOTAL BUDGET: DISC 2, Round 1 2016	
Funded	$9,442,218
Not Funded	$44,356,631

App #	Title	Score	Median	SD	Low	High	Budget	Tier	T1	T2
DISC2-09098	Use of Human iPSC-derived Endothelial Cells for Calcific Aor	94	95	3	85	95	$2,400,048	1	13	0
DISC2-08874	Novel Rejuvenated T Cell Immunotherapy for Lung Cancer	90	90	1	85	90	$2,217,264	1	15	0
DISC2-08824	CRISPR/Cas9 nanoparticle enabled therapy for Duchenne M	89	90	3	80	95	$2,150,400	1	14	1
DISC2-09123	Immunotherapy for HIV infection using engineered hematop	85	85	8	70	95	$1,586,934	1	9	6
DISC2-09032	MSC delivery of an artificial transcription factor to the brain a	85	85	10	70	100	$1,087,572	1	8	7
DISC2-09073	Autologous cell therapy for Parkinson's disease using iPSC-d	83	85	17	25	95	$2,354,226	2	10	4
DISC2-08990	Human Heart-on-a-chip for disease modeling and developin	83	82	6	70	92	$1,008,325	2	7	8
DISC2-08982	Scalable, Defined Production of Oligodendrocyte Precursor	81	85	9	65	90	$1,848,462	2	10	4
DISC2-08957	Dynamic scaffolding system to enhance lineage-specific diffe	79	80	4	70	85	$780,097	2	2	13
DISC2-09095	A human platform to model microcephaly caused by the Zika	77	75	6	65	85	$1,039,760	2	3	12
DISC2-08862	Microenvironment for hiPSC-derived pacemaking cardiomyc	76	75	7	65	90	$1,722,833	2	4	11
DISC2-09018	iPS Glial Therapy for White Matter Stroke and Vascular Deme	75	75	3	70	82	$1,910,640	2	0	14
DISC2-09140	Ex vivo and in vivo genome editing of hematopoietic stem ce	74	75	7	60	90	$2,676,240	2	2	12
DISC2-08846	Novel anti-inflammatory agents in cardiac stem cell-based th	74	75	7	60	85	$2,200,800	2	2	13
DISC2-09100	Efficacy of Personalized Exosomes from iPSC-derived Cardio	72	70	4	65	80	$2,210,438	2	0	15
DISC2-08953	CRISPR/dCas9 mutant targeting SNCA promoter for downre	72	70	16	45	95	$1,975,173	2	5	10
DISC2-09054	Tracking cardiomyocyte progenitor cells delivered to myoca	71	70	4	60	75	$1,001,957	2	0	14
DISC2-09027	Stem-Cell Derived Placental Exosomes for Diabetes Therapy	71	70	14	40	90	$1,384,350	2	3	12
DISC2-09064	Immuno-protected Engineered Islets for Type I Diabetes Tre	69	70	10	50	85	$2,195,679	2	1	14
DISC2-09150	IPSC-Based Diagnostic Platform for Neurogenetic Disorders	65	65	2	60	70	$1,083,600	2	0	15
DISC2-08972	A predictive stem-cell based tool to accelerate Staphylococ	62	60	11	50	90	$1,111,578	2	1	14
DISC2-09087	Engineering cardiovascular tissue for heart tissue replaceme	60	60	0	60	60	$1,376,588	2	0	15
DISC2-09115	Using human embryonic stem cells to develop novel approa	60	60	0	60	60	$1,171,980	2	0	14
DISC2-08960	Nano-electrode based electrophysiology system for the eval	59	60	6	45	75	$380,857	2	0	15
DISC2-09075	Microelectrophysiological Assessment of Pharmacology usin	59	60	4	50	65	$899,328	2	0	15
DISC2-09082	Preclinical development of engraftable human liver stem cell	59	60	6	50	65	$2,217,264	2	0	15
DISC2-09004	Small Molecules for Fibrosis and Myocardial Regeneration	55	60	24	20	80	$2,163,596	2	0	14
DISC2-08966	A stem cell model of ApoE genotype and Abeta42-depende	54	50	11	40	80	$1,093,260	2	0	15
DISC2-08888	Employing neural precursor-like cells to promote remyelinat	54	52	4	50	60	$1,566,117	2	0	14
DISC2-09154	Developing a stem cell-enabled peripheral blood-based dia	53	55	13	15	70	$1,035,720	2	0	14
DISC2-08807	Development of a small molecule therapy to ameliorate prot	48	50	9	35	70	$2,071,300	2	0	15
DISC2-08820	Cardiogenic Human Extracellular Matrix Proteins for Optimiz	41	40	11	25	60	$1,671,476	2	0	15
DISC2-08830	Pluripotent Redox Reporter Stem Cell Lines for Real-Time Im	28	20	14	20	60	$835,000	2	0	15
DISC2-09152	Development of Neuronal Autophagy Inducers (NAI) to Trea	25	1	33	1	80	$1,369,987	2	0	14

Public Summary for DISC2-08807

Application #	DISC2-08807
Title (as written by the applicant)	Development of a small molecule therapy to ameliorate protein-RNA aggregation in Amyotrophic lateral sclerosis
Research Objective (as written by the applicant)	We propose to discover a bioavailable small molecule therapeutic to reduce aberrant protein-RNA aggregates in ALS.
Impact (as written by the applicant)	ALS, with the potential of broadly impacting neurodegenerative diseases such as PD and AD where protein-RNA aggregates are also disease-causing.
Major Proposed Activities (as written by the applicant)	• Identify more potent compounds with activity in wild-type and mutant IPSC-derived motor neurons. • Identify even more potent compounds with in vitro properties consistent with oral availability and CNS penetration. • Identify compounds that are candidates for proof of concept *in vivo*.
Statement of Benefit to California (as written by the applicant)	The incidence of ALS is two per 100,000 people, and it is estimated that as many as 30,000 Americans may have the disease at any given time. There are no effective therapies of ALS to-date. Our research aims to develop a small molecule therapeutic that is aimed to treat ALS, which may be applicable to other neurological diseases that heavily impact Californians.
Funds Requested	$2,071,300
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	8	2
Is the rationale sound?	0	12	3
Is the proposal well planned and designed?	0	12	3
Is the proposal feasible?	2	10	3

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Drugs that limit the formation of stress granules could be reasonably identified using this approach.
- Identifying novel neuroprotective path was appealing.
- The application is interesting but premature.

Concerns

- The applicants never show the consequence of decreased SG in patient derived MN. Do the lead drugs prevent degeneration or affect MN functions?
- The plan is to test the drugs in an animal model of ALS. The readouts are not clear, and the expected outcome is not discussed.
- The applicant seems to work under the assumption that prevention of stress granule formation is a very upstream event that prevents all other pathways leading to pathology. The rationale for this assumption is not clearly laid out.
- Verification of drug efficacy on patient lines is limited to the determination of stress granules and abnormal RNA expression patterns. No functional assays are proposed to test the health of patient derived neurons in the absence or presence of lead drugs.
- The team did not show preventing stress granules was neuroprotective - this was considered a major flaw.
- The proposed approach does not add much new leverage to a drug-development strategy that has already been extensively explored.
- There is no evidence provided that modifying stress granule accumulation will have any benefits, even *in vitro*.
- In a first screen, some compounds were found that seem to inhibit stress granule accumulation, but it is not clear if any of these compounds would be of potential clinical utility.
- As there is no hypothesis beyond decreasing stress granule density based on drug screens and drug optimization, there are no alternatives provided except more drug screens.
- There is a lack of thought towards devising relevant biological endpoints.

Additional Comments

- The proposal needs more time to be developed. Reviewers suggested that the team gather more preliminary data on iPSCs.

Public Summary for DISC2-08820

Application #	DISC2-08820
Title (as written by the applicant)	Cardiogenic Human Extracellular Matrix Proteins for Optimizing and Enhancing Cardiac Stem Cell Therapy
Research Objective (as written by the applicant)	We propose to demonstrate that a protein found in the developing human heart will cause the scar to shrink when injected post heart attack and also will help enhance survival on injected stem cells.
Impact (as written by the applicant)	To deliver an adjunct therapy that is not yet available to enhance survival of stem cells injected into the heart.
Major Proposed Activities (as written by the applicant)	• Demonstrate that injecting this protein causes the scar size to decrease after a heart attack. • Demonstrate that injecting this protein along with stem cells enhances the survival and growth of stem cells in the heart following a heart attack.
Statement of Benefit to California (as written by the applicant)	Heart failure secondary to heart attacks is a leading cause of morbidity and mortality in California. Although stem cells are a promising therapy, the engraftment and survival of stem cells in a heart after a heart attack is very low. This is a significant bottleneck in the field and any therapies to enhance this with our proposed protein will significantly enhance the survival and benefit of stem cell therapies for California patients and beyond.
Funds Requested	$1,671,476
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	9	2
Is the rationale sound?	2	11	2
Is the proposal well planned and designed?	1	13	1
Is the proposal feasible?	2	11	2

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposal has a good rationale and is addressing an important problem.

Concerns

- The major issue with the application is that there is no evidence that the protein co-injected with ESCs, in any model, results in improved outcomes. Simply put, there is not much evidence that the proposed protein is the key to engraftment of cells in heart muscle.
- The lack of significant preliminary data to support this hypothesis is a weakness.
- The lack of sound rationale for the use of this protein to enhance cell therapy is a weakness. In particular, the mechanism of cell clearance is not well understood in the chronic state and is not feasible in the acute peri-infarct state.
- The PI seems to lack expertise in large animal models. The PI's publication record in the research area is worrisome.
- There is no evidence that the therapy improves outcomes.
- Pig studies are incomplete and premature. There is no way to have 40 animals with a complete data set starting with only 40 animals. Dose and timing of doses are missing. Cell retention is not addressed.
- Analysis of data from pig studies is missing and there appears to be no expertise to do the experiments. For example, who will do the electrical analysis? Also, 40 pigs over two years is modest.
- No funds are provided to the UCLA Arrhythmia Group, where the pig experiments will be performed. It is unclear how/who will be performing these experiments. Since all experiments use the pig model system, this is a major issue with the proposal.
- Gaps in the plan for the present and for translating subsequently reduced enthusiasm.
- Key letters of support are missing.

Additional Comments

- The ESC work appears to be an afterthought. The cell culture of ESCs in the preliminary data does not support the proposed Aim 2 pig experiment, which uses iPSC-derived CPCs.
- The PI must show that in the mouse model that the proposed protein + ESCs results in improved outcomes prior to initiating the two Aims (both using pigs). There is no reason to do the pig experiment when it is unknown if CPCs co-injected with the protein will work in the mouse model system.

Public Summary for DISC2-08824

Application #	DISC2-08824
Title (as written by the applicant)	CRISPR/Cas9 nanoparticle enabled therapy for Duchenne Muscular Dystrophy in muscle stem cells
Research Objective (as written by the applicant)	Gene correction of muscle stem cells
Impact (as written by the applicant)	These studies will develop a gene editing based therapy for one of the most prevalent lethal childhood disorders called Duchenne Muscular Dystrophy (DMD).
Major Proposed Activities (as written by the applicant)	• To identify the best mesoporous silica nanoparticle (MSNP)-CRISPR candidates for CRISPR/Cas9 plasmid delivery in vitro to muscle stem cells. • To identify the best chemoattractants (MSNP-STEM) candidates suitable for delivery of the optimal chemo attractant that enables stem cell migration *in vitro*. • To identify the optimal MSNP-CRISPR and MSNP-STEM candidates from biodistribution studies after systemic injection. • To determine the efficiency of MSNP-CRISPR and MSNP-STEM approaches for delivering CRISPR/Cas9 platform to the stem cell niche. • To identify the MSNP delivery strategy that results in restoration of functional dystrophin protein and improved muscle strength after long-term satellite cell correction or reconstitution.
Statement of Benefit to California (as written by the applicant)	Duchenne Muscular Dystrophy is a progressive muscle wasting disorder with life expectancy of approximately age 20 with incidence of 1 in 5,000 live male births. Because it is a chronic disorder, this disease is devastating to families, involves extensive medical expenses and loss of employment for caregivers. School-age children require a classroom aid and an IEP. A treatment for DMD could reduce health care costs, time lost from work and burden on the public school system.
Funds Requested	$2,150,400
GWG Recommendation	***Recommended for funding, if funds are available.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 89

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	90
Standard Deviation	3
Highest	95
Lowest	80
Count	15
Number of reviewers who scored 85-100	14
Number of reviewers who scored 1-84	1

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	14	0	1
Is the rationale sound?	12	0	3
Is the proposal well planned and designed?	13	0	2
Is the proposal feasible?	11	1	3

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- This is a novel therapeutic approach to a devastating disease, and the proposal contains strong preliminary data.
- This project might actually produce results that could benefit patients on a time scale of years rather than decades.
- These techniques may also be used as generalized strategies for other genetic diseases.
- The nanoparticle approach is unique and promising, and the strong team is particularly well suited to execute these experiments. The novelty was a major score driver.
- It is likely that MSNP-based CRISPR delivery and stem cell homing systems will be useful for stem cell- or gene editing based therapies.
- The path for a therapeutic treatment of Duchenne Muscular Dystrophy (DMD) is clear, and the candidate will be ready for preclinical testing if the objectives are met.
- Prodigious amounts of preliminary data show protocols are well developed. CRISPR/Cas9 system can generate appropriate DYS construct that can restore DYS expression and function in differentiated DMD muscle.
- The dual pronged approach is powerful.
- The homing of the nanoparticles in the inflamed tissue is impressive.

Concerns

- The major concern is the uncontested efficacy of both *in vivo* and *ex vivo* stem cell treatments.
- Inducing larger DMD deletions to convert DMD to Becker muscular dystrophy (BMD) is not really curative therapy.

Additional Comments

- Application would have been improved by proposing functional assays of contractility for proof of integration and functional restoration, but this was not a major score driver.

Public Summary for DISC2-08830

Application #	DISC2-08830
Title (as written by the applicant)	Pluripotent Redox Reporter Stem Cell Lines for Real-Time Imaging of Oxidative Stress
Research Objective (as written by the applicant)	We propose to create stable stem cell lines which integrate genetically encoded fluorescent redox reporters to quantify oxidation in cultured pluripotent and differentiating cells.
Impact (as written by the applicant)	Redox cell lines would impact all levels of work including basic research, culture medium development, drug testing with disease-in-a-dish models, and quality control in translational/clinical labs.
Major Proposed Activities (as written by the applicant)	• We would first construct and optimize gene cassettes for expression of redox reporters. Cassettes would be validated in transiently transfected cells. • We would then construct viral vectors for delivering gene cassettes, and validate the viral vectors by construction of at least one stable reporter line with an optimized gene cassette. • We would next create 5 additional stable redox reporter cell lines, one line from human embryonic stem cells, 2 from iPSC controls, and 2 from iPSC from Alzheimer's patients. • We would validate the first redox cell line created using live cell imaging coupled with video bioinformatics software tools, gene expression arrays, and flow cytometry. • Five additional redox reporter lines (1 hESC line and 4 iPSC lines) will be validated with live cell imaging/video bioinformatics software tools, gene expression arrays, and flow cytometry. • We will next test the 6 redox reporter lines in a rapid neurogenesis assay to establish that the reporters function properly during differentiation and in a cell differentiated from the reporter line.
Statement of Benefit to California (as written by the applicant)	The redox reporter lines have the potential to accelerate many facets of stem cell research. For example, they could be used to improve culture conditions, develop better media, screen drugs for dish-in-a-dish applications, test for toxicity of additives/chemicals, explore mechanisms of pathogenesis in degenerative disease, and provide a quality control platform for translational and clinical labs. All of these application would accelerate bringing stem cell therapies to California' citizens.
Funds Requested	$835,000
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	0	14	1
Is the rationale sound?	1	12	2
Is the proposal well planned and designed?	0	14	1
Is the proposal feasible?	2	11	2

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The preliminary data supports that they can develop redox sensor proteins but does not extend beyond this.

Concerns

- As this is more of a basic science project building redox sensor proteins, it is hard to make the case that it addresses an unmet medical need.
- It is unclear what unmet medical need is being addressed. Measuring oxidative stress is important in some contexts, which could result in the reporter plasmids being useful. However, since most therapies use specific cells lines, each lab would need to create their own lines.
- The project does not demonstrate the urgency to develop a stem cell-based therapy for disease.
- This is a complex system that is not clearly an improvement over current techniques.
- It is not clear what the benefit of this approach is over available dyes.
- The bandwidth of the reporter system is not clear.

Additional Comments

- The idea that redox changes are important in cell function is very well established, and more sensitive tools for such analysis would be welcome. No argument is made, or data presented, that this approach will be more sensitive.
- It is not known if the reporters work in human ESC/iPSCs.
- In Aim 3, fast neuron differentiation from hESCs is shown. It is unclear what type of neurons are shown. The Principal Investigator appears to be classifying these cells as neurons based on their morphology and expression of B-tubulin III.

Public Summary for DISC2-08846

Application #	DISC2-08846
Title (as written by the applicant)	Novel anti-inflammatory agents in cardiac stem cell-based therapy
Research Objective (as written by the applicant)	We propose to use a novel lead compound that increase the survival, engraftment and maturation of transplanted hiPSC-derived cardiomyocytes by reducing inflammation in the host myocardium.
Impact (as written by the applicant)	Myocardial infarction results in inflammatory responses that inhibit stem cell survival. We propose to increase the survival of the transplanted stem cells by reducing inflammation using a novel drug.
Major Proposed Activities (as written by the applicant)	• Select a lead candidate that is orally available and test the in vivo efficacy and safety profiles. • Perform a proof-of-concept to demonstrate the efficacy of the combinatorial therapy of hiPSC-CM stem cell therapy with the lead candidate.
Statement of Benefit to California (as written by the applicant)	Cardiovascular disease remains the leading cause of death in California and is responsible for more deaths than all cancers combined. Current therapeutic strategies using cell-based therapy to combat heart failure have not produced full restorative functions. A high rate of transplanted stem-cell loss has been observed due to ischemic environment and inflammation in the host environment. Our proposed study will address this major setback in the current stem cell therapies.
Funds Requested	$2,200,800
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 74

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	75
Standard Deviation	7
Highest	85
Lowest	60
Count	15
Number of reviewers who scored 85-100	2
Number of reviewers who scored 1-84	13

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	4	6
Is the rationale sound?	4	5	6
Is the proposal well planned and designed?	3	7	5
Is the proposal feasible?	5	4	6

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Great unmet need, some preliminary data shows evidence of increasing cell retention with the drug.
- This reviewer had much enthusiasm for this approach that had a prodigious amount of preliminary data including evidence that novel anti-inflammatory agents enhance incorporation of stem cell cardiomyocytes.
- The team is extraordinarily strong comprising clinical, tissue, physiological and chemical expertise.

Concerns

- The main concern about this application is that there is a disconnect between the anti-inflammatory properties of the new drugs and the actual mechanism (lack of retention) of a stem cell therapy for heart failure.
- Some concerns were raised in review about quality of preliminary data.
- Some preliminary data presented is not correct, like the pressure-volume loops on sham mice appear to be of a myocardial infarction (MI) mouse model. Echo data does not represent percent fractional shortening.
- Application for stem cell based therapies for heart failure is not clear.

Additional Comments

- The proposed tool could probably be developed, but there is little reason to think it addresses a central problem in stem-cell research.
- Trying to fit the proposal to a RFA but not really designed for it.
- Information of dosing levels, timing of dosing, and how anti-inflammation drugs will be useful. Also, information on when iPS cells from the patient would actually be ready, e.g. long time after MI if injected, will be critical to success.

Public Summary for DISC2-08862

Application #	DISC2-08862
Title (as written by the applicant)	Microenvironment for hiPSC-derived pacemaking cardiomyocytes
Research Objective (as written by the applicant)	This proposal investigates the effects of the microenvironment on the development and maintenance of pacemaking function in hiPSC-derived cardiomyocytes.
Impact (as written by the applicant)	Pacemaking function of hiPSC-derived cardiomyocytes is lost over time. Sustainability of pacemaking function of these cells is critical for engineering a biopacemaker.
Major Proposed Activities (as written by the applicant)	• Determine the effects of matrix scaffolds on the differentiation and maintenance of pacemaking function in hiPSC-derived cardiomyocytes. • Determine the effects of fibroblasts on the differentiation and maintenance of pacemaking function in hiPSC-derived cardiomyocytes. • Determine the appropriate hiPSC-derived cardiac cells to be subjected to the microenvironment for efficient yield of pacemaking hiPSC-derived cardiomyocytes. • Induce vascularization in tissue constructs in vivo to sustain pacemaking tissue construct. • Test sustainability of a functional pacemaking tissue construct *in vivo*.
Statement of Benefit to California (as written by the applicant)	Over 350,000 patients a year in the U.S. require an electronic pacemaker to restore their heart rhythm. The annual healthcare burden amounts to $20 billion. Repeated surgeries to replace battery and electrical parts generate additional costs and suffering for the patients. A biopacemaker engineered from human stem cell-derived pacemaking cells can overcome problems associated with electronics and improve the quality of life for the pacemaker recipient while reducing cumulative health care costs.
Funds Requested	$1,722,833
GWG Recommendation	***Not recommended for funding.***
CIRM Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 76

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	75
Standard Deviation	7
Highest	90
Lowest	65
Count	15
Number of reviewers who scored 85-100	4
Number of reviewers who scored 1-84	11

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	3	5
Is the rationale sound?	5	3	7
Is the proposal well planned and designed?	4	5	6
Is the proposal feasible?	1	3	11

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- It is likely that ECM-based signaling from the human heart SA node can direct differentiation of iPSC-CM into pacemaker cells.
- This is a very innovative idea that could potentially yield important translational and mechanistic information. In particular, the investigators provide an innovative hypothesis regarding the role of the microenvironment on cardiomyocyte subtype specification.
- Objective 1 is well designed to test the proposed hypothesis.
- Differentiation of myocytes into SA nodal cells using environmental cues is potentially transformative.
- From a basic science perspective, the proposal is innovative and addresses an interesting problem.

Concerns

- The role of cardiac fibroblasts is less obvious, and the rationale for using tissue specific fibroblasts is not adequately justified. The use of animal ECMs and fibroblasts for cardiac differentiation of human iPSCs and *in vivo* studies in a mouse model are convenient but unlikely to support translation to clinical applications.
- Preliminary data are not yet convincing that ECM and fibroblasts from the SA node will be sufficient to direct subtype specification.
- The rationale for *in vivo* studies in a mouse model is less convincing given that heart rates for mouse and human pace-making tissues are vastly different.
- The subcutaneous model in Objective 2 is not physiologically relevant and it is not evident how this will enable translation.
- Some weakness in approach such as the use of mouse model, and the lack of strong preliminary data supporting proof of concept mildly hamper enthusiasm for this proposal.

Additional Comments

- This proposal may not be ideal for the Quest Program.
- Porcine SA nodes are not at all human like. A different animal for the scaffold may improve outcomes.

Public Summary for DISC2-08874

Application #	DISC2-08874
Title (as written by the applicant)	Novel Rejuvenated T Cell Immunotherapy for Lung Cancer
Research Objective (as written by the applicant)	Through this project, we would like to evaluate how this T-iPSC-based immunotherapy that we have developed can eliminate lung cancer cells effectively in vivo using xenografted SCID mice.
Impact (as written by the applicant)	This novel T-iPSC-based immunotherapy will provide another effective treatment for lung cancer and possible other malignancies by supplying unlimited number of young and active CTLs.
Major Proposed Activities (as written by the applicant)	• Peptides synthesis for EGFR mutation hot spots and selection of the peptides with affinity binding assay. • Patient lung cancer/ blood cell culture and xenograft establishment in SCID mice for establishing tumor model. • Peptide responsive T cell selection, IPS induction and T cell re-differentiation and expansion (rejCTL) for cell-based immunotherapy. • Transfusion of patient specific rejCTL cells into lung cancer grafted mice to treat tumors. • Evaluation of the efficacy of rejCTL cell therapy by observing tumor sizes in xenografted mice. • Statistical analysis and conclusion for this novel cell-based cancer treatment and contact FDA for initiation of a clinical trial.
Statement of Benefit to California (as written by the applicant)	Lung cancer is known to cause the highest fatality rate. California State and citizens suffer similarly as the US and worldwide do. A fairly common HLA allele, e.g. HLA A0201 presents in up to 50% of California populations. Thus, we can provide an 'off the shelf' therapy for most of cancer patients. As a California based institute, we will succeed this research and pioneer this frontier cell-based immunotherapy, and conduct a possible clinical trial through CIRM funding.
Funds Requested	$2,217,264
GWG Recommendation	***Recommended for funding, if funds are available.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 90

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	90
Standard Deviation	1
Highest	90
Lowest	85
Count	15
Number of reviewers who scored 85-100	15
Number of reviewers who scored 1-84	0

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	15	0	0
Is the rationale sound?	13	1	1
Is the proposal well planned and designed?	15	0	0
Is the proposal feasible?	14	0	1

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The approach is at the forefront of cancer immunotherapy technology. This proposal represents an exciting possibility of rejuvenating exhausted lung cancer peptide-MHC I-specific T cells for use in cancer immunotherapy.
- The following were considered key strengths:
  - Inclusion of a suicide strategy to allow elimination of the infused rejuvenated T cells if that become necessary is a strength.
  - Identification of lung cancer-specific MHC I-binding peptides to serve as targets for immunotherapy.
  - An inexhaustible supply of T cells to fight patient-specific tumors over long term would be extremely beneficial.
- The development of adoptive immunotherapy for solid tumors may be highly significant.
- The proposal cleverly uses reprogramming as a tool.
- The potential for wider use is a strength here.
- The Principal Investigator is major leader in field.
- This is a strong application with high level of enthusiasm and it contains outstanding potential.

Concerns

- No critical concerns were expressed by the GWG.

Additional Comments

- Doubt was expressed regarding the clinical practicality of this type of fallback immunotherapy for a cancer in which the primary therapies are not very effective. However, if this proposal is viewed as a model for new modes of immunotherapy, the project is worth supporting.
- The proposal is based on recently published work.

Public Summary for DISC2-08888

Application #	DISC2-08888
Title (as written by the applicant)	Employing neural precursor-like cells to promote remyelination and tissue repair in multiple sclerosis
Research Objective (as written by the applicant)	We will investigate the influence of neural precursor-like cells (NPLCs) on remyelination and autoimmunity in autoimmune models of multiple sclerosis (MS).
Impact (as written by the applicant)	There are currently no clinically approved treatments for Progressive MS. We will determine if NPLCs induce repair or instead influence autoimmune cells as a first step toward their use to treat MS.
Major Proposed Activities (as written by the applicant)	• We will identify the gene expression "fingerprint" of hNPLCs that induce the strongest clinical recovery in autoimmune and non-inflammatory models of MS. • We will identify the molecules released from hNPLCs that 1) affect anti-inflammatory T cells, and 2) induce repair in damaged neurons. • We will determine if anti-inflammatory T cells that accumulate in the central nervous system following hNPLC transplantation have a role in promoting neurological repair in an autoimmune MS model. • We will characterize the impact of pro- and anti-inflammatory T cells on gene expression within the damaged CNS to determine how these immune cells affect repair mechanisms.
Statement of Benefit to California (as written by the applicant)	Multiple sclerosis afflicts many Californians, a disease that typically presents in early adulthood. It is a highly debilitating disease for which there is currently no cure. While there are therapies that limit autoimmune damage, these therapies are ineffective for progressive forms of MS. We will characterize a novel cell population we have identified called neural precursor-like cells (NPLCs) that may facilitate neurological repair and clinical recovery in progressive MS patients.
Funds Requested	$1,566,117
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	5	5
Is the rationale sound?	0	8	6
Is the proposal well planned and designed?	0	9	5
Is the proposal feasible?	1	8	5

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The potential impact on an unmet need is high.
- The topic is significant; the problem of repair and remyelination in MS is important.
- The proposal contains an interesting concept with strong preliminary work.

Concerns

- The cells they propose to use are very poorly defined.
- The rationale for using their cells to modify regulatory T cell function as compared with bone-marrow derived cells (whether MSCs or the Athersys cells) is not even considered - but why would you use iPSC-derivation of cells when you can use cells that are as easily obtained as bone-marrow derived cells?
- There is no characterization of hNPLC and no clear definition of the need of rejection, injury or inflammation to elicit hNPLC-mediated repair.
- MS phenotype in the brain not addressed. It is not clear what neuronal precursor-like cells are.
- Rationale is inadequately integrated with the large, relevant literature on MS.
- The lack of experimental detail reduces enthusiasm.
- There are multiple issues related to experimental approach and logic.

Additional Comments

- Previous work in the Miller laboratory has shown that MSCs work in this model by producing hepatocyte growth factor as a key modulator and has also shown that MSCs from patients with multiple sclerosis do not provide benefit. Both of these are relevant pieces of information and experimental needs that are ignored in the proposal.
- Some element examining myelination in brain would have improved application.

Public Summary for DISC2-08953

Application #	DISC2-08953
Title (as written by the applicant)	CRISPR/dCas9 mutant targeting SNCA promoter for downregulation of alpha-synuclein expression as a novel therapeutic approach for Parkinson's disease
Research Objective (as written by the applicant)	Discovery of a novel therapeutic candidate for Parkinson's disease which modifies gene expression using human stem cell-derived neurons to halt the neurodegenerative disease process.
Impact (as written by the applicant)	Stopping the neurodegenerative process of Parkinson's disease is a critical unmet medical need. Our approach is based on novel gene engineering technology that modifies expression of key target genes.
Major Proposed Activities (as written by the applicant)	• Identification and engineering of therapeutic candidates that downregulate expression of target gene in human stem cell-derived neuronal precursor cells. • Measurement of target gene downregulation in human stem cell-derived dopaminergic neurons with assessment of phenotype rescue. • Testing downregulation of target gene using relevant pre-clinical model containing endogenous gene regulatory regions. • Development of a Target Product Profile for advancement of the therapeutic candidate for CIRM partnering opportunity: translational research projects (TRAN). • Preparation for stage appropriate regulatory meetings for subsequent CIRM pre-clinical application. Develop regulatory strategy with CIRM Clinical Advisory Panel.
Statement of Benefit to California (as written by the applicant)	Estimated 36,000-60,000 people in the State of California are affected with Parkinson's disease which is a neurodegenerative disease that causes a high degree of disability and financial burden for our health care system. This collaborative project will provide substantial benefits and values to the state of California and its citizens by developing new therapeutic candidates for the treatment of Parkinson's disease enabled by stem cell technologies and gene therapy.
Funds Requested	$1,975,173
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 72

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	70
Standard Deviation	16
Highest	95
Lowest	45
Count	15
Number of reviewers who scored 85-100	5
Number of reviewers who scored 1-84	10

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	4
Is the rationale sound?	7	2	6
Is the proposal well planned and designed?	4	2	9
Is the proposal feasible?	2	5	8

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- This application is very novel using a technology that really is in its infancy. However, should the technology work, it has the potential to be disease modifying for the treatment of Parkinson's disease. Therefore, the proposal should be classified as high risk/high reward.
- This proposal is clearly translational.
- I thought this was a very well written grant with a strong investigator with a good track record with a logical, well-thought out scientific method and approach.
- CRISPR/Cas9 is exactly the new kind of technology to deploy on problems like this.
- It is a great, innovative idea. The proposal is a venturesome approach to a hard problem. Although it is high risk, the proposal is worth a try.
- This proposal would add a new dimension to the current therapeutic approaches to Parkinson's disease.
- The proposal contains an interesting hypothesis. Targeting alpha-synuclein in Parkinson’s diease is novel, interesting and has a sound rationale
- This is an alternative approach that is worth trying. It is not clear if this will work, but the science is excellent.

Concerns

- The Principal Investigator would appear to have very limited expertise in CRISPR/dCas9 technology, a technology which underpins the success of this proposed program of work. This creates a slight hesitation and makes this challenging project difficult to take to fruition.
- The spread of the virus is a concern. What will happen if there is too little or too much downregulation of alpha synuclein? There is no information provided on how this might be addressed.
- There are not enough preliminary data covering realistically translatable issues of specificity of the proposed agent.
- Concerns were raised about the possibility of wide distribution of the vector based on Figure 6 of the grant. It is also possible that this represents transport in axons. The issue of spread should be resolved.
- Absence of preliminary data showing alpha-synuclein can be knocked down by the CRISPR-Cas9 dampened enthusiasm. In absence of preliminary data, there are doubts that work can get done within the timeline.

Additional Comments

- All reviewers agreed this was good science. Concerns center on not enough preliminary data, not being translational, or not reaching a clinical goal in 2 years. But given the fairly modest amount of funding offered by this RFA, the proposal set reasonable goals and would advance CIRM's mission.
- Why wait to fund this great idea? What if the applicant does not have enough support to generate enough preliminary data to make it to a next round of funding? Will the idea wither?
- This proposal seems like it is more appropriate as a pilot application.

Public Summary for DISC2-08957

Application #	DISC2-08957
Title (as written by the applicant)	Dynamic scaffolding system to enhance lineage-specific differentiation of pluripotent stem cells
Research Objective (as written by the applicant)	This study will develop a cell culture system which will increase the differentiation efficiency of stem cells to target cell types for enhanced therapeutic applicability.
Impact (as written by the applicant)	The technology to be developed in the proposed study will more efficiently control stem cell behaviors to produce clinically applicable cells in a cost-effective manner.
Major Proposed Activities (as written by the applicant)	• Optimize multi-functional scaffolds for enhanced controllability and biocompatibility. • Develop a high-throughput cell culture system with tunable scaffolds. • Validate the performance of the cell culture system on stem cell differentiation.
Statement of Benefit to California (as written by the applicant)	This project seeks to advance the safety and effectiveness of the use of stem cells for regeneration of damaged tissues in patients' body by developing a novel technology. The project speaks directly to the mission of CIRM, particularly to improve human health for California's rapidly growing population by stem cell-based therapies. The commercialization of the full-scale system would benefit the people in California with the financial impact of increased employment and tax revenues.
Funds Requested	$780,097
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 79

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	80
Standard Deviation	4
Highest	85
Lowest	70
Count	15
Number of reviewers who scored 85-100	2
Number of reviewers who scored 1-84	13

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	4	4
Is the rationale sound?	8	1	6
Is the proposal well planned and designed?	7	2	6
Is the proposal feasible?	8	2	5

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The biomaterials aspect is state of the art, and the strength in biomaterials was an impressive aspect of this proposal.
- Technology is innovative, and there is an excellent scientific basis in dynamic modulation of substrate stiffness using novel biomaterial.
- The proposal contains strong preliminary data and has a high feasibility of achieving device design metrics in the course of the study.
- The application is clear and well written.

Concerns

- The major issue is that the application is not focused on a specific issue in human disease and will not produce a technology and/or cell population that will specifically be used to address a major issue in human health.
- A drawback to the application is that the machine will only function in “steps”. There is no way to control stiffness/softness in a gradient.
- Unclear that the proposal addresses a real need in stem-cell research. Even if successful, uptake of the device the project would attempt to develop would probably be low.
- Translational component of research was lacking. There is no specific critical bottleneck identified.

Additional Comments

- The path to translation is not clear. While the device is achievable, the integration of this device into cell manufacturing would be challenging. However, it does have potential applications in discovery science.
- The project is well constructed but it is not focused on a specific outcome beyond development of a cell culture system that uses mechano-modulation.
- Dynamic control is important.

Public Summary for DISC2-08960

Application #	DISC2-08960
Title (as written by the applicant)	Nano-electrode based electrophysiology system for the evaluation of drug-induced cardiotoxicity using human stem cell-derived cardiomyocytes
Research Objective (as written by the applicant)	A novel electrophysiology system for automated, scalable, intracellular recording of action potential from human stem cell-derived cardiomyocytes.
Impact (as written by the applicant)	The current gap in automated, high-precision tool for the electrophysiological characterization of heterogeneous human SC-derived cardiomyocytes, and their application in cardiotoxicity assessment.
Major Proposed Activities (as written by the applicant)	• Determine user requirements of the proposed tool for the electrophysiological assessment of drug-induced cardiotoxicity using human stem-cell derived cardiomyocytes (hSC-CMs). • Design and verify a prototype system based on the user requirements. • Validation of the prototype system for the assessment of drug-induced cardiotoxicity by examining known arrhythmogenic compounds on human stem cell-derived cardiomyocytes.
Statement of Benefit to California (as written by the applicant)	The application of human stem-cell derived cardiomyocytes (hSC-CMs) for diseases modeling, drug discovery and toxicity assessment has been challenged by the lack of automated, high-precision methodology for the functional characterization of these cells, and the phenotypic heterogeneity among hSC-CMs . This research aims to produce a novel electrophysiology system that provides scalable, functional phenotyping of hSC-CMs, specifically for applying hSC-CMs for assessment of drug-induced toxicity.
Funds Requested	$380,857
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	2	13	0
Is the rationale sound?	4	11	0
Is the proposal well planned and designed?	0	12	3
Is the proposal feasible?	4	9	2

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The project is feasible with a prototype already developed and significant preliminary data illustrating the ability to perform electrophysiologic measurements in this device.

Concerns

- It is unclear if the proposed device would actually address a critical need of experimentalists.
- The design would need to be better tested under real world conditions such as a cell culture environment.
- The maturity of the cells may be a problem. Without wider testing of different drugs, it is not clear if the technology will actually work.
- The proposal would be strengthened if some market data were already obtained. The proposal lacks clear design metrics and it has not been established that a sufficient user base exists.
- Problem facing better safety screens is not heterogeneity so much as immaturity, but this is not considered in application.
- Not clear that recording from individual cells would provide better assay of e.g. torsadogenic potential of drugs compared to MEA or other syncytial platforms.

Additional Comments

- While understanding the users' need is important, no staff is identified to carry out this aim which may be one of the more important aspects of this proposal.
- Easier measurement of electrophysiology of iPSC-cardiomyocytes would be beneficial, but this is not one of the major translational roadblocks for these cells.
- Voice of the consumer research should precede a project such as this one.

Public Summary for DISC2-08966

Application #	DISC2-08966
Title (as written by the applicant)	A stem cell model of ApoE genotype and Abeta42-dependent neurodegeneration
Research Objective (as written by the applicant)	Isogenic panel of genetically modified hES cells useful for Alzheimer's drug screening and cellular basis of ApoE allele type to neurodegeneration.
Impact (as written by the applicant)	Most Alzheimer's experimental models do not degenerate, the major cellular phenotype and clinical correlate of the disease. As a result therapeutic approaches to modify degeneration are not available.
Major Proposed Activities (as written by the applicant)	• Establish a panel of human embryonic stem cells that can be useful for testing drugs that can slow or eliminate the rate of neurodegeneration underlying the progressive nature of Alzheimer's disease. • Develop methodology that can be applied to embryonic stem cell analysis of Alzheimer's type neurodegeneration. • Establish the cellular action of ApoE genotype with respect to Alzheimer's type neurodegeneration.
Statement of Benefit to California (as written by the applicant)	Nearly 1 million California citizens will be afflicted with Alzheimer's in the near future. No effective treatments are currently available to eliminate the untold suffering of patients and their caregivers. Our stem cell based model holds promise for two important advances: The cell platform we develop can be used to screen for new drugs directly targeting neurodegeneration and they will provide a scientific rationale for future stem cell based treatment strategies.
Funds Requested	$1,093,260
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below.

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	8	2
Is the rationale sound?	0	9	6
Is the proposal well planned and designed?	0	12	3
Is the proposal feasible?	1	11	3

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The applicants generated a stem cell model of Ab1-42- dependent neurodegeneration using genome editing of human ES cell lines. They also produced a genetically identical Ab1-40 control line. Excitingly, only the Ab1– 42 line undergoes progressive neurodegeneration in culture. This is promising.
- The cell system that is developed offers a potentially novel platform for drug screening and cell specific analysis of AD pathology but the cell population used (motor neurons) is not a relevant cell type to model AD.

Concerns

- Whether they can make the right types of cells or can use cells for therapeutic discovery is not established.
- The description of astrocytes is greatly oversimplified and does not even consider the potential relevance of different kinds of astrocytes. Yet, in individuals with two ApoE4 alleles, there is regionality of degeneration indicating that regional biology may be very important.
- The current system uses motor neuron differentiation protocols, but such cells are not the target in Alzheimer's. The need to generate cortical cholinergic neurons is discussed but no data is provided that this is possible.
- What the project lacks is any demonstration that the model provided is of any utility in terms of drug discovery. As multiple agents have been reported that prevent A1-42 toxicity in vitro, the lack of examination of such agents in their model system is striking in its absence.
- The applicant proposes to generate a number of pure neuronal or astrocytic cultures. This is a vital requirement for the co-culture approach. No preliminary data are provided that the applicants can generate consistently highly pure populations.
- Their definition of ND in preliminary data is not robust, appears to rest on cell scoring on relatively generic markers by manual methods, and could be subject to multiple interpretations, for example, failures in specification vs survival. Rationale behind using spinal motor neurons is very weak as they have an extremely tenuous relationship to disease since these cells are not affected.
- Cultures are contaminated with "non-neural cells".
- Unclear that the proposed disease-in-a-dish model is an optimum way to characterize the interesting phenotypic differences the investigators have discovered between cells with genotypes that differ in Alzheimer's risk. Motor neuron is not seen as relevant model system for AD.

Additional Comments

- The work is at too early a stage to determine if this would address an unmet medical need. There are multiple untested steps that would be required to answer in the affirmative.
- The authors point out that one of the earliest pathologies are a disruption of the autophagy- endosomal- lysosomal pathway. While they provide preliminary data of up-normal AEL structures in their edited cells, the quantification and analysis of this important pathway is not part of their characterization and optimization.
- Highly important problem and some aspects of AD seem to emerge in this system but are premature to this RFA since the preliminary data fail to support premise.

Public Summary for DISC2-08972

Application #	DISC2-08972
Title (as written by the applicant)	A predictive stem-cell based tool to accelerate Staphylococcus aureus vaccine development
Research Objective (as written by the applicant)	Development of a stem cell-based tool designed to assess human adaptive immune responses in vivo to predict whether or not a candidate vaccine is likely to succeed in clinical trials.
Impact (as written by the applicant)	All staph vaccine trials to date have failed and the lack of predictive tools is the major bottleneck. We propose to develop a highly predictive tool for staph vaccine development.
Major Proposed Activities (as written by the applicant)	• We will develop a "personalized" humanized mouse that can accept T and B cells from an individual by using peripheral blood hematopoietic stem cells isolated from that individual. • We will transfer into the mice blood immune cells from an individual previously vaccinated with a pneumococcal vaccine, and challenge the mouse with pneumococcus. This will serve as tool validation. • There is mounting evidence that select T cells could protect against Staph. For positive control, we will make these cells in culture and test if they protect against Staph in the personalized mice. • Individuals who chronically harbor Staph in the nose are partially protected against severe infection. We will put their T and B cells into the mice and test their protective function against Staph.
Statement of Benefit to California (as written by the applicant)	Staph aureus including Methicillin-resistant Staph (MRSA) infections are frequently in the news. They represent some of the most common infections in California and the US and are often severe or fatal in the elderly. There are many vaccines that have shown efficacy in animals, but none so far have worked in humans. Our tool would help prioritize vaccines that are most likely to succeed in clinical trials and therefore would accelerate the pace of developing an effective Staph vaccine.
Funds Requested	$1,111,578
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 62

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	60
Standard Deviation	11
Highest	90
Lowest	50
Count	15
Number of reviewers who scored 85-100	1
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	7	3
Is the rationale sound?	1	9	5
Is the proposal well planned and designed?	1	8	6
Is the proposal feasible?	0	10	5

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Staph aureus is a major pathogen, and the development of vaccine strategies would be significant.
- This proposal addresses an important problem. It is high risk but a basically rational approach.

Concerns

- There is concern that transfer of human T cells into the human-HSC-modified mice will cause GVHD precluding conclusions about immunity to S. aureus.
- There was a failure to deal sufficiently with the
  - relevant literature about mouse studies of Th17 cell-based immunity to S. aureus.
  - issue that human HSC-modified mice will still contain many mouse components that could reduce the relevance of this humanized model.
- The model is unlikely to be informative.
- Some reviewers were unclear if pneumococcus was sound approach since its biology is different from that of staphylococcus. The use of pneumococcus as a positive control is not useful as the method of pathogenesis of Staph Aureus and S. pneumoniae is different.
- Graft v. host problems not adequately addressed.
- It is unclear if this is a novel proposal.

Additional Comments

- No relevant comments were made by the GWG.

Public Summary for DISC2-08982

Application #	DISC2-08982
Title (as written by the applicant)	Scalable, Defined Production of Oligodendrocyte Precursor Cells to Treat Neural Disease and Injury
Research Objective (as written by the applicant)	The goal of this proposal is to develop an optimized, scalable process to manufacture high quality oligodendrocyte precursor cells (OPCs) from human pluripotent stem cells for treating human disease.
Impact (as written by the applicant)	OPCs have therapeutic potential for spinal cord injury, restoration of cognitive function after cancer radiation therapy, inherited demyelinating disease, and potentially multiple sclerosis.
Major Proposed Activities (as written by the applicant)	• To engineer human embryonic stem cell lines with fluorescent protein reporters to quantify differentiation into oligodendrocyte precursor cells (OPCs). • To use a high throughput system to screen thousands of cell culture conditions and thereby optimize a chemically-defined three-dimensional culture for differentiation into OPCs. • To validate the capacity of the differentiated oligodendrocyte precursor cells to remyelinate neurons in culture and in the nervous system. • To scale up this cell manufacturing system in a bioreactor for future translation towards preclinical and clinical studies.
Statement of Benefit to California (as written by the applicant)	This proposal will accelerate the development of a stem cell therapy to treat patients with demyelinating conditions, a serious unmet medical need. Also, the PI has a strong record of translating research towards clinical development within industry, particularly within California. Finally, this project will expose young scientists within a large stem cell center to highly interdisciplinary training at the interface of science and engineering, thereby enhancing our California workforce.
Funds Requested	$1,848,462
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team recommends this application for funding.***

Scoring Data

Final Score: 81

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	85
Standard Deviation	9
Highest	90
Lowest	65
Count	14
Number of reviewers who scored 85-100	10
Number of reviewers who scored 1-84	4

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	3	4
Is the rationale sound?	9	1	4
Is the proposal well planned and designed?	8	1	5
Is the proposal feasible?	8	1	5

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposal is outstanding and contains an excellent manufacturing strategy, innovative scale up methodology, and an innovative screening process.
- Highly innovative technologies are proposed. For example, the 3D scalable technology is highly innovative, and the applicant-developed high throughput screening (HTS) platform is impressive.
- It is an impressive quantitative proposal.
- This is a clever approach and HTS could lead to candidate with big impact. The thermoresponsive polymer was clever as well.

Concerns

- As this attempt to generate large numbers of oligodendrocyte precursor cells (OPCs) is still realistically in a pilot project phase, it is hard make the case of a high likelihood of impact.
- This is one of many attempts by different groups to generate human OPCs via induced pluripotent stem cell (iPSC) or related technologies. There is no evidence that this group is competitive in respect to generating OPCs, and the quantitative data presented suggests they are far from their goal.
- There is no evidence that this will lead to a translation-relevant candidate, and the analysis of cells is sufficiently superficial and thus far non-quantitative as to raise concerns.
- There is little in the way of hypothesis-based ideas about what to do if the planned approach does not work.

Additional Comments

- The proposal is a promising way of producing populations of oligodendrocyte precursor cells. It is less clear whether success would have broad impact.
- It is difficult to argue this work is in agreement with the urgency of CIRM's goals as the biological aspects of the project are still largely in a pilot phase.

Public Summary for DISC2-08990

Application #	DISC2-08990
Title (as written by the applicant)	Human Heart-on-a-chip for disease modeling and developing new strategies to treat cardiac diseases
Research Objective (as written by the applicant)	This proposal will develop patient specific 'heart-on-a-chip' diagnostics that will have a significant impact on the early screening of drugs used to manage hypertrophic cardiomyopathy.
Impact (as written by the applicant)	Patient specific 'heart-on-a-chip' diagnostics will significantly reduce the cost of bringing a new drug candidate to market while improving efficacy.
Major Proposed Activities (as written by the applicant)	• To develop patient specific 'heart-on-a-chip' diagnostics for drug discovery. • To validate the 'heart-on-a-chip' diagnostic to predict responses to clinical medicines used to manage hypertrophic cardiomyopathy. • To develop a Target Product Profile for the 'heart-on-a-chip' diagnostic. • To develop a manufacturing plan for the 'heart-on-a-chip' diagnostic.
Statement of Benefit to California (as written by the applicant)	One in 500 Californians suffer from hypertrophic cardiomyopathy (HCM), a leading cause of sudden cardiac death in young adults. There are no drugs that target specific disease alleles of HCM. We have developed patient specific 'heart-on-a-chip' diagnostics that will have a significant impact on the development of drugs used to manage hypertrophic cardiomyopathy. If successful, we can reduce the cost and time needed to bring new drugs to market, thereby improving the lives of many Californians.
Funds Requested	$1,008,325
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 83

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	82
Standard Deviation	6
Highest	92
Lowest	70
Count	15
Number of reviewers who scored 85-100	7
Number of reviewers who scored 1-84	8

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	3	6
Is the rationale sound?	4	3	8
Is the proposal well planned and designed?	11	1	3
Is the proposal feasible?	9	2	4

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Excellent preliminary work demonstrating integration of physiologic analysis into 3D cardiac tissue screening platform.
- The proposal contains very high commercial translational potential in complementing existing *in vitro* and *in vivo* models for drug screening.
- The focus on the translation is strong, and translation to a final product is very good.
- A major unmet medical need would be addressed by new drugs to treat heart failure although this seems far down the road.
- The device is excellent and the microfluidic model is strong.

Concerns

- There are concerns about whether genetic hypertrophic cardiomyopathy model will be predictive of aging-related heart failure.
- It is not clear if the model is fully representative of the complexity of the disease.
- Evidence that cells show certain qualities of cardiomyopathy is a strength, but whether they are sufficiently mature to manifest as a meaningful disease model is uncertain. The application of this system to a disease with a long developmental time course is premature.
- The lack of differentiation in my [the reviewer's] view is an issue; the cells are still immature.

Additional Comments

- The application does not clearly describe what drug responses would be assessed.

Public Summary for DISC2-09004

Application #	DISC2-09004
Title (as written by the applicant)	Small Molecules for Fibrosis and Myocardial Regeneration
Research Objective (as written by the applicant)	Candidate is a small molecule that stimulates/recruits endogenous stem cells to regenerate myocardial mass & reduce fibrosis as the 1° MOA for repair/regeneration & is being developed for unmet needs.
Impact (as written by the applicant)	MI is the most prevalent cause of heart failure (HF) in the US. 25-40% that suffer extensive ventricular injury develop HF. Our approach will overcome the heterogenous nature of stem cell implants.
Major Proposed Activities (as written by the applicant)	• Produce ≥ 1 gr of ITD and (+)-ITD in > 95% purity. This will be done under non-GLP practices for Goals #2 & 4 studies. We have backup synthetic strategies to mitigate against any problems. Make patch. • Do mouse efficacy studies with ITD & (+)-ITD. ITD (or more likely (+)-ITD) will be efficacious in the mouse MI model, confirmed with mRNA markers decreased to 40-50% the control MI group values. • GLP prep of ITD (or (+)-ITD) & patch. Do efficacy studies in a swine MI animal model with ITD or (+)-ITD to decrease fibrosis, preserve myocardial mass & improve ejection fraction by echocardiography. • Do IND-enabling pharmaceutical & ADMET studies, chemical & metabolic stability, safety studies, bioavailability of patch + ITD (or (+)-ITD) to the heart. Do histopathology of heart after patch + ITD. • Nominate ITD or (+)-ITD as a lead compound for advancement pending efficacy in pigs. Summarize the findings in preparation for pre-IND discussions with the FDA & ultimately writing an IND.
Statement of Benefit to California (as written by the applicant)	We will develop a new heart disease therapy. In CA, the incidence of heart failure for those > 65 yrs is 1/100, with a 5 year mortality rate of ~50% & costs of $3.7 billion/yr. Current therapies preserve cardiac function rather than regenerate muscle cells. That heart muscle regenerates, once controversial, has now been verified. Human cardiac cell regeneration is too low to offset the loss that occurs in heart disease. We will develop new materials to enhance endogenous myocardial regeneration.
Funds Requested	$2,163,596
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	5	3
Is the rationale sound?	0	10	4
Is the proposal well planned and designed?	2	7	5
Is the proposal feasible?	2	6	6

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The novel TGF beta inhibitor (ITD) has significant clinical and translational promise.
- There is a streamlined plan to evaluate ITD's effects on improving heart function.
- The compound has likely effects on fibrosis, but it is likely to result in significant cardiac regeneration.
- Emphasis on controlling fibrosis is a positive.
- The preclinical models are a strength; the plan is rational and could end in IND.

Concerns

- The inhibition of fibrosis is very important for cell therapy, but there is no evidence of cell recruitment. The proposed would be improved by adding the cells and the drug to the patch.
- The application does not address the fact that there is proven cardiac stem or progenitor cell. The term “cardiac progenitor cells” is used loosely. There is no definition of these cells, or how they may regenerate the myocardium.
- Prevention of fibrosis has no direct link to cardiac regeneration. In fact, there are many antifibrotic therapies that are in clinical practice, such as ACEI for example, that markedly decrease fibrosis, but they do not regenerate the myocardium.
- Preliminary data does not convincingly show that ITD recruits stem cells or improves myocardial function.

Additional Comments

- The patch needs to be reformulated to an injectable form. The patch approach to deliver ITD compound to enhance recruitment and survival of cardiomyocytes and preventing fibrosis involves an open chest procedure, but future developments could overcome limitations.
- The completeness of the study from safety, tox and use of the animal models is great. The mouse studies seem under powered. Loop recorders should be used in the swine. The number of MRI in swine seems excessive.

Public Summary for DISC2-09018

Application #	DISC2-09018
Title (as written by the applicant)	iPS Glial Therapy for White Matter Stroke and Vascular Dementia
Research Objective (as written by the applicant)	The studies will develop an iPS-glial enriched progenitor cell line (iPS-GEPs) for brain repair in white matter stroke.
Impact (as written by the applicant)	This treatment will be directed toward white matter stroke, a common stroke subtype and cause of dementia, for which no therapy exists; and will develop an imaging biomarker to track this therapy.
Major Proposed Activities (as written by the applicant)	• Efficacy. 1) Test efficacy of iPS-GEPs in chronic white matter stroke; 2) Test the efficacy of transplant location; 3) Test the dose response; 4) Test optimum dose and timing in aged mice. • Mechanism of Action. 1) Identify in vivo expression profile of iPS-GEPs during period of tissue repair; 2) Correlate behavioral recovery effect with levels of candidate molecular systems in iPS-GEPs. • Assay Development. Based on preliminary RNAseq studies of iPS-GEPs: 1) Develop identity assays for iPS-GEPs; 2) Develop purity assays for iPS-GEPs; 2) Develop activity assays for iPS-GEPs. • Biomarker Development. 1) Develop structural MRI biomarker of iPS-GEP repair of damaged white matter; 2) Develop resting state MRI biomarker of enhanced brain connectivity.
Statement of Benefit to California (as written by the applicant)	White matter stroke is common and progressive, leads to vascular dementia (the second most common form of dementia), and accelerates Alzheimer's Disease. White matter stroke is strongly age-associated: by age 80 all of us will have these lesions in our brain. There is no therapy for white matter stroke. This research develops a stem cell therapy that repairs the brain in white matter stroke, and a process whereby this repair therapy can be tracked in MRI to monitor the disease and recovery.
Funds Requested	$1,910,640
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 75

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	75
Standard Deviation	3
Highest	82
Lowest	70
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	1	4
Is the rationale sound?	3	4	7
Is the proposal well planned and designed?	2	5	7
Is the proposal feasible?	1	3	10

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- It is likely that stem cell-based treatment of white matter stroke has a very high therapeutic potential. The proposal as described will tackle important clinical questions including dose response, injection chronic time points and *in vivo* imaging biomarker development.
- Glial precursor exposed to iron chelator drives productions of astrocytes; targeting the white matter is a strength.

Concerns

- The application is based on one human iPSC line and will be tested on a mouse model that likely will not be sufficient to accelerate clinical translation. Including other iPSC lines plus a control mouse iPSCs and human ESCs would be beneficial.
- The reproducibility of the observations is not possible to discern from the application. As presented, it appears that everything has been done with a single cell line. Is this is the best cell line of many attempts, the only cell line of many attempts, or a representative of a robust outcome?
- The application does not sufficiently address the problem of astrocyte heterogeneity. It seems that discussing astrocytes as a single population of cells is oversimplifying the issue. What kind of astrocytes are being generated? Do outcomes differ in different brain regions (as the precursors are quite migratory)? Using the well-defined astrocyte induction molecules that have been extensively studied, what kinds of astrocytes are generated even *in vitro*?
- There is also a concern characterization of the populations is largely conducted at the population level, providing no information on the purity that is provided by analysis of antigen expression by immunofluorescence analyses (for example).
- Evidence of multiple cells lines to bolster reproducibility would have generated more confidence in the approach; lack of correlation between biomarker and functional recovery in time was also a weakness.
- The relevant cell biology is inadequately understood. What is known about the cell type proposed for therapeutic use suggests their effects would lack specificity.

Additional Comments

- There is much to like in this proposal, but there are important items of information that are missing, which decreases enthusiasm for the proposal.
- The proposal would be improved if more in-depth tissue analysis would have been carried out.

Public Summary for DISC2-09027

Application #	DISC2-09027
Title (as written by the applicant)	Stem-Cell Derived Placental Exosomes for Diabetes Therapy
Research Objective (as written by the applicant)	We will use unique human embryonic stem cells that make placenta, to produce a novel therapeutic, placental exosomes, for inducing the regeneration of insulin-producing cells in people with diabetes.
Impact (as written by the applicant)	This therapeutic will be used to drive the regeneration of pancreatic beta cells in people with both type 1 and type 2 diabetes.
Major Proposed Activities (as written by the applicant)	• Generate human placental cells from human embryonic stem cells. • Characterize stem-cell derived placental cells and compare to normal placental cells. • Produce exosomes from stem-cell derived placental cells. • Characterize the stem-cell derived exosomes and compare to normal placental exosomes. • Test the function of exosomes from stem-cell derived placental on human insulin-producing cells (beta cells) in culture and transplanted into mice.
Statement of Benefit to California (as written by the applicant)	The prevalence of both major forms of diabetes, type 1 and 2, is increasing in California. The economic cost of diabetes in California was estimated at $27.55 billon in 2012. Beyond the economic costs, the personal costs for patients and families include the daily burden and loss of flexibility imposed by glucose management and hypoglycemia, and the long-term harm caused by the microvascular and macrovascular complications. To prevent these problems, we need better therapies for diabetes.
Funds Requested	$1,384,350
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendaiton	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 71

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	70
Standard Deviation	14
Highest	90
Lowest	40
Count	15
Number of reviewers who scored 85-100	3
Number of reviewers who scored 1-84	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	4	4
Is the rationale sound?	2	6	7
Is the proposal well planned and designed?	2	6	7
Is the proposal feasible?	2	5	8

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The major strengths are the team of investigators and the novelty and potential impact of the proposed approach for Type I diabetes and for Type II diabetes.
- This is an exciting concept with huge clinical potential.
- While there is a significant risk of failure (it may not be possible to generate placental exosomes in the needed quantities), the proposal outlines a clear path forward toward a promising, plausible treatment for diabetes.
- The use of exosomes is novel; an exosomal approach to address diabetes is an intriguing idea.
- The goal of making new therapies for diabetes is highly important; diabetes is an incurable disease and this approach may advance the field toward treatment.

Concerns

- The main weakness is the feasibility of Aim 1, which is premature.
- The application seems premature and based on many assumptions.
- The proposal lacks sufficient preliminary data suggesting feasibility of deriving TSCs and cytotrophoblasts from human ESCs. This has not been achieved even from mouse ESCs; the cited human study has not been independently confirmed or reproduced.
- Some concern was expressed by the reviewers about the uncertainty of obtaining cytotrophoblasts.

Additional Comments

- Success depends on generation of trophoblasts.
- It is likely that exosome-based signaling is an important natural pathway regulating beta cell function during pregnancy.
- There is a high dependence of Aims 2 and 3 on the feasibility and success of Aim 1.

Public Summary for DISC2-09032

Application #	DISC2-09032
Title (as written by the applicant)	MSC delivery of an artificial transcription factor to the brain as a treatment for Angelman Syndrome
Research Objective (as written by the applicant)	Mesenchymal stem cells will be used to deliver an artificial transcription factor to neurons in the brain to treat a genetic disease.
Impact (as written by the applicant)	It could lead directly to a treatment for Angelman Syndrome, but the approach could be used to alter gene expression in almost any brain disorder. It could overcome the brain delivery bottleneck.
Major Proposed Activities (as written by the applicant)	• Prepare the MSC delivery system (month 1 – month 6). • Rescue and analysis of on-target molecular phenotypes in "YFP-mice" (month 6 – month 12). • Rescue and analysis of the behavioral phenotypes in "AS-mice" (month 12 – month 24). • Analysis of the off-target molecular phenotypes in "YFP-mice" (month 18 – month 24).
Statement of Benefit to California (as written by the applicant)	Brain disorders are responsible for more years lost to disability than any other medical condition. For example, autism spectrum disorder (ASD) in the US is estimated to affect 1 in 68 children. The need for effective treatments cannot be understated. Molecular therapeutics pioneered to understand and treat rare single-gene disorders such as Angelman Syndrome will provide the tools and methods that will ultimately be used to address the more common complex brain disorders.
Funds Requested	$1,087,572
GWG Recommendation	***Recommended for funding, if funds are available.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	85
Standard Deviation	10
Highest	100
Lowest	70
Count	15
Number of reviewers who scored 85-100	8
Number of reviewers who scored 1-84	7

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	12	2	1
Is the rationale sound?	7	1	7
Is the proposal well planned and designed?	9	1	5
Is the proposal feasible?	7	3	5

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The application is focused on a new method to correct the single gene defect associated with Angelman syndrome. While this disease is rare, the applicants propose that the methodology could be adapted to other brain disorders and therefore addresses a highly unmet medical need.
- The success of delivering enough artificial transcriptions factor (ATF) seems to depend on the ability of MSC to enter the brain, cross the blood-brain barrier, generate the protein, and deliver the protein without causing inflammation. This is an ambitious goal but worth pursuing.
- The impressive preliminary results demonstrate the proof-of-concept for restoring the production of Ube3a. Alternative treatments for Angelman Syndrome patients are currently lacking. The proposed strategy is presented in high detail and in a convincing manner. The planned experiments (Milestones) address every aspect to prove the feasibility of the project.
- Potential pitfalls are appropriately discussed.

Concerns

- A weakness here is the missing explanation in the Western blot analysis “appearance of a particular Ube3a isoform”. Is this isoform also in the wildtype?
- It is not clear how a transcription factor can be secreted from the cells.
- Stronger emphasis on mechanism would have strengthened the application

Additional Comments

- The method is in principle based on very strong preliminary data, but the effective delivery and distribution of the ATF in the brain generates a therapeutic hurdle. The authors will address this hurdle by using MSCs as a vehicle.
- Angelman Syndrome is a good target for this therapeutic approach owing to its devastating phenotype.

Public Summary for DISC2-09054

Application #	DISC2-09054
Title (as written by the applicant)	Tracking cardiomyocyte progenitor cells delivered to myocardial infarct using novel MRI technology
Research Objective (as written by the applicant)	Our primary objective is to develop the unique technical ability to non-invasively and longitudinally visualize stem cell grafts following injection.
Impact (as written by the applicant)	Investigators are currently unable to verify cardiac stem cell locations and persistence after delivery. This project will address this unmet need.
Major Proposed Activities (as written by the applicant)	• Cell labeling and in vitro characterization studies. • Successful implementation of 19F/1H MRI on a 3T clinical MRI scanner at UCSD. • First MI swine injected with stem cells and imaged using MRI. • Completion of injection and longitudinal imaging of a cohort of swine. • Data analysis and dissemination.
Statement of Benefit to California (as written by the applicant)	California leads the nation in supporting stem cell research with the aim of finding cures for major diseases. A common need to accelerate the translation of these potentially lifesaving therapies are methods to image the behavior and movement of cells following delivery. Recent progress in magnetic resonance imaging (MRI) demonstrate the feasibility of non-invasive monitoring of transplanted cells. These MRI cell tracking methods will be applied to new a stem cell therapy for heart disease.
Funds Requested	$1,001,957
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 71

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	70
Standard Deviation	4
Highest	75
Lowest	60
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	2	4
Is the rationale sound?	4	4	6
Is the proposal well planned and designed?	1	7	6
Is the proposal feasible?	0	5	9

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- Overall, the label appears promising and the proposal is well written. But since the label appears to be good only for short term imaging it dampens my enthusiasm.
- The strengths of this application are the background of the investigators and the area of research that is an unmet need.
- A method to track stem cells *in vivo* represents an unmet need.

Concerns

- There are concerns about the persistence of the label. The duration for monitoring cell markers is far too short to achieve experimental relevance. Long-term engraftment is the process that correlates most strongly with clinical efficacy of cell therapies.
- Since the coil and software are not in place, delays here would impact the timeline of the study.
- Concerns have been raised regarding the fidelity of the signal and whether the indicator would stay within the cell of interest.
- In addition, another concern has been raised regarding the likelihood that these indicators would provide a positive signal for weeks and months.
- Concern was expressed that signal in stem cells may be excreted from stem cells and taken up by others; what is needed is a mechanism to trap them in the cell.

Additional Comments

- Using MMP could add another layer to the experiment. If no label was detected, would it be because the MMP did not work or was the label an issue? A second more tried and true approach of cell injection would eliminate the problem.
- When and if this technology goes to a large-animal model, the initial tests should involve cell transplantations in which the behavior of the infused cells is already well understood from other types of studies.

Public Summary for DISC2-09064

Application #	DISC2-09064
Title (as written by the applicant)	Immuno-protected Engineered Islets for Type I Diabetes Treatment
Research Objective (as written by the applicant)	The expected outcome of these studies is a cellular therapeutic for Type I Diabetes: engineered human islets for transplant into patients, surpassing the function of beta cells or progenitors alone.
Impact (as written by the applicant)	The proposed studies would address key bottlenecks in cell replacement therapy for Type I Diabetes: issues with cell function, and optimization of cellular encapsulation devices for delivery *in vivo*.
Major Proposed Activities (as written by the applicant)	• Determine the optimal composition of human embryonic stem cell (hESC)-derived engineered islets *in vitro*. • Demonstrate function of engineered islets *in vivo* in immunodeficient animals. • Optimize cellular encapsulation of engineered islets. • Demonstrate immuno-protection of engineered islets in the encapsulation device.
Statement of Benefit to California (as written by the applicant)	Type I Diabetes (T1D) is a significant burden in California, especially for children; according to estimates provided by the California Diabetes Program, ~2.3 out of every 1,000 children between the ages of 5-19 in California had diagnosed diabetes in 2008, with 83% having T1D. Research proposed here would represent a significant step towards the holy grail of T1D treatment: a therapy for patients without the need for the administration of insulin, frequent blood testing, or immunosuppression
Funds Requested	$2,195,679
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 69

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	70
Standard Deviation	10
Highest	85
Lowest	50
Count	15
Number of reviewers who scored 85-100	1
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	4	3
Is the rationale sound?	1	9	5
Is the proposal well planned and designed?	0	10	5
Is the proposal feasible?	1	10	4

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The main strengths are the team of investigators, the impact of the work, and Aim 1.
- The rationale that to be clinically effective, ESC-derived beta cells must be engineered into islet-like clusters using 3D culture with varying niche components (endothelium, fibroblasts, pericytes, ECM) is sound and convicting.
- The proposal contains good biology in optimizing the environment of the beta cells.
- Impressive junior investigator with high productivity.
- Preliminary data were convincing.

Concerns

- The main weaknesses are the lack of experimental details and preliminary data relating to Aim 2 and Aim 3. Aim 3 is not well described as no data is provided for the aim.
- Also, Aim 1 appears trivial and not enough details are provided. There are insufficient details on endothelial, mesenchymal cells, pericytes, and microvascular endothelial cells that are key niche elements for composing islet-like organoids in Aim 1.
- Potential pitfalls and alternative experiments are not outlined in the proposal.
- The use of an immunoisolation system has not been shown to work in the past 50 years. The emphasis on this aspect is not worthwhile.
- There is no track record of this team working together.

Additional Comments

- It was suggested that the applicant refocus the proposal on Aims 1, 2 and include experimental details and potential pitfalls/alternative strategies.
- Components of this system (islet-cluster engineering and encapsulation) need more development before it makes sense to do a “go-for-broke” test of the whole system.

Public Summary for DISC2-09073

Application #	DISC2-09073
Title (as written by the applicant)	Autologous cell therapy for Parkinson's disease using iPSC-derived DA neurons
Research Objective (as written by the applicant)	Autologous human dopaminergic neurons derived from patient-specific induced pluripotent stem cells
Impact (as written by the applicant)	Parkinson's disease
Major Proposed Activities (as written by the applicant)	• Characterize differentiation from all 10 patient cell lines. • Characterize functionality of patient neurons matured *in vitro*. • Immunogenicity assessment. • Cryopreservation feasibility testing. • Investigate dose response *in vivo*. • Detect dopamine release *in vivo*.
Statement of Benefit to California (as written by the applicant)	Thousands of Californians suffer from the degenerative effects of Parkinson's disease, a disease for which there is no cure. There is hope, however, that stem cells could provide the key to providing long-term relief. Our study seeks to treat patients with cells derived from their own stem cells, a process which could be applied to other diseases such as diabetes and heart disease and could potentially be used to the benefit of many of the citizens of California.
Funds Requested	$2,354,226
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team recommends this application for funding.***

Scoring Data

Final Score: 83

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	85
Standard Deviation	17
Highest	95
Lowest	25
Count	14
Number of reviewers who scored 85-100	10
Number of reviewers who scored 1-84	4

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	2	3
Is the rationale sound?	5	3	6
Is the proposal well planned and designed?	4	5	5
Is the proposal feasible?	7	3	4

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposal is a highly focused project in a clinically relevant area.
- This is a well-designed proposal and the preliminary data are for the most part strong. A particular strength is the careful characterization of the cells, the analysis of immunoresponse, and the *in vitro* outcomes.
- The project is innovative and explores a problem that has proven nearly intractable. It is risky but worth a try.
- The proposal contains careful analysis of cells and has strong reproducibility.
- Two animal models with behavior demonstrates functional recovery, which was a significant strength.

Concerns

A concern was raised related to graft survival – the numbers of tyrosine hydroxylase (TH) neurons -- and innervation. The applicant should relate the number of surviving neurons found in each grafted rat presented in the behavior study to the number of injected cells. In addition, the applicant should show that the TH neurons that the applicant proposes to use have the capacity to exhibit significant fiber outgrowth into the host striatum from grafted stem cell-derived TH neurons. Without evidence of fiber outgrowth, there is some concern about feasibility. It would be important for this to be achieved as an early milestone.

- A major concern is the *in vivo* analysis of the graft. The applicants need to show the level of transplant integration and survival in their experiments. As stated, Figure 14B shows limited integration raising major concerns as to the efficiency of the transplant. If integration is not achieved, it is likely that the behavioral outcomes are not related to the grafted cells.
- Concern was expressed that the differentiation protocol does not give rise to dopamine neurons that grow many (essential) axons into the striatum after transplantation.
- Cryopreservation of stem cell-derived neural precursors or neurons is challenging. The applicant should demonstrate that their cryopreservation protocol generates neurons that can survive transplantation, or at least prolonged survival in culture (not just acute expression of molecular markers).

Additional Comments

- The reviewers strongly recommended that an early milestone that defines integration and cell survival in the already transplanted animals be in place. The next milestone would depend on the outcome of this analysis.
- The first milestone needs to show cell survival quantification, fiber outgrowth and integration. The applicant needs to show complex sensorimotor recovery after transplantation. These two milestones must be achieved before proceeding.

Public Summary for DISC2-09075

Application #	DISC2-09075
Title (as written by the applicant)	Microelectrophysiological Assessment of Pharmacology using Labchip Electroencephalogram (MAPLE) for neurological diseases
Research Objective (as written by the applicant)	We propose to discover a high-throughput method for tailoring drug therapy and drug discovery for patients with genetic seizure disorders.
Impact (as written by the applicant)	This method would obviate the current time-consuming, trial-and-error method of determining the best combination of drugs to treat any given patient's seizures.
Major Proposed Activities (as written by the applicant)	• Differentiation of seizure patient derived iPSCs into a robust population of neural stem cells (month 1 to month 12). • Production of high-sensitivity electrophysiological analysis chips (month 3 to month 22). • Differentiation of seizure patient derived NSCs into electrically active neurons (month 3 to month 22). • Demonstration of robust, reproducible, and phenotype specific neuronal electrical activity in the electrophysiological analysis chips (month 6 to month 18). • Examination of the drug responsiveness of phenotype specific neurons in the electrophysiological analysis chips (month 12 to month 24)
Statement of Benefit to California (as written by the applicant)	Currently, a patient's seizures tend to be controlled with multiple, rather than single, drugs. Finding the right drug combination is educated trial and error and can take many months. Our MAPLE device, using the patient's own cells, will allow us to quickly arrive at the proper drug combination without subjecting the patient to lengthy trial and error drug exposures.
Funds Requested	$899,328
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	2	7	6
Is the rationale sound?	1	6	8
Is the proposal well planned and designed?	0	9	6
Is the proposal feasible?	3	5	7

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The concept is a good one.

Concerns

- As the project is still at a feasibility stage, it is a long way to make this argument that this would significantly impact medical care.
- Limited preliminary data.
- There is no proof of link to clinical efficacy.
- There is limited anticonvulsant data on patient population.
- There is a lack of preliminary data that supports the primary assumption.
- No demonstration of the library of patients that correlate the phenotypes with the read-out.
- Not clear how this technology is better than what is currently available.

Additional Comments

- There is an untested assumption that the in vitro measurements have relevance to the clinical situation.
- Related to the above point, the key experiment is not conducted. This would be to make cells from patients with a known history of failed response to one or two drugs and successful response to another drug, making IPSC-derived neurons and then demonstrating the ability to observe the same outcomes in vitro as seen in the clinic.
- There is a need to build stronger positive controls into the research plan.

Public Summary for DISC2-09082

Application #	DISC2-09082
Title (as written by the applicant)	Preclinical development of engraftable human liver stem cells derived from embryonic stem cells: long-term efficacy, purity and safety profile
Research Objective (as written by the applicant)	We will develop purified populations of human liver stem cells from embryonic stem cells as a candidate therapeutic for treatment of end-stage liver failure.
Impact (as written by the applicant)	If we succeed in developing human liver stem cells as a therapeutic candidate, this would establish an abundant source of cells for future treatment of patients with end-stage liver failure.
Major Proposed Activities (as written by the applicant)	• To assess whether hESC-derived LivSCs can engraft long-term in mouse models of liver injury and robustly improve survival. • To define the in vivo biodistribution and cell growth kinetics of engrafted hESCs-derived LivSCs and their putative mechanism of action in rescuing liver injury. • To purify transplantable hESC-derived LivSCs and quantify their homogeneity by discovering specific cell-surface markers. • To evaluate the safety of hESC-derived LivSCs and their lack of tumor forming-ability.
Statement of Benefit to California (as written by the applicant)	Liver failure is one of the top 12 leading causes of mortality in the U.S. Currently, the only effective treatment for end-stage liver failure is liver transplantation. Due to limited donor livers, many patients with liver failure do not receive this treatment and pass away. If we successfully develop engraftable human liver stem cells, this will meet an immense unmet clinical need to obtain a consistent source of hepatocytes for transplantation into human patients with liver failure.
Funds Requested	$2,217,264
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	7	6	2
Is the rationale sound?	1	10	4
Is the proposal well planned and designed?	0	11	4
Is the proposal feasible?	1	11	3

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The experiments are well explained, and have a high success of being completed, but appear to be based on published research that is proving difficult to reproduce.
- Donor livers are currently used. Development of liver cells or even liver stem cells would overcome a huge roadblock in the field.
- Team is strong and likely to make significant advances in this area

Concerns

- The major fault with the present application is the lack of assessment of mature liver functions and activities. There is little evidence of mature liver function in the cells this team produces.
- They have not developed a useful test of mature liver function such as ammonia metabolism, mature CYP450 gene expression and function. They do not even know how far from a normal human liver the cells are that they produce.
- The engraftment in the mouse is quite low and does not seem to be sustained. Thus, there is little in this application to suggest that they have anything that will be useful for translation in the near future.
- They have no clear idea, nor any experienced person to help them translate a product to the clinic to treat liver disease.
- There are insufficient criteria for whether the differentiated cell types would actual be hepatocytes.
- The absence of sufficient evidence that hepatocytes have mature liver function in terms of metabolic activities dampens enthusiasm.

Additional Comments

- This is an ambitious proposal. The experiments are not likely to be completed by the end of the two-year funding period.
- Key concerns were the actual function of the cells, lack of data supporting the quality and utility. Strong expertise in parts of the techniques (FACS surface marker screens), but lack of understanding of the liver biology is apparent. The whole concept of the LiverSCs remains to be tested, is controversial and not widely accepted in the field.

Public Summary for DISC2-09087

Application #	DISC2-09087
Title (as written by the applicant)	Engineering cardiovascular tissue for heart tissue replacement
Research Objective (as written by the applicant)	This proposal will generate heart tissue for replacement of damaged heart tissue from a heart attack.
Impact (as written by the applicant)	Current stem cell injections are only moderately reparative. Currently, no viable tissue substitute for damaged heart tissue is available.
Major Proposed Activities (as written by the applicant)	• Generation of high numbers of cells for building tissue. • Assemble the heart cells into contracting tissue. • Build tissue stretching device that can be used to study tissue integration in the lab. • Integrate tissue with patterned blood vessels. • Examine heart repair using a small animal model.
Statement of Benefit to California (as written by the applicant)	More than a million Americans have heart attacks each year, usually leaving permanent damage to the heart muscle. Because heart cells exhibit only limited proliferative capabilities, the derivation of heart cells from stem cells is a critical part of strategies of heart repair. However, the direct injection of cells alone is not sufficient. Engineering cardiovascular tissue could replace the damaged heart tissue, and for many patients, reduce the need for a whole heart transplant.
Funds Requested	$1,376,588
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	60
Standard Deviation	0
Highest	60
Lowest	60
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	2	5	8
Is the rationale sound?	2	5	8
Is the proposal well planned and designed?	0	7	8
Is the proposal feasible?	1	5	9

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The project addresses a crucial medical need and there is promise for the use of iPSC-derived cardiac cells in regenerative therapies.
- This proposal addresses an important problem.

Concerns

- The plan is broad and addresses many of the roadblocks in the field, but there is not a novel, deep approach that suggests improvement over prior work in this area.
- The proposal lacks preliminary data supporting the concepts of use of 3D tissue alignment, endothelial cell incorporation, or application of mechanical forces.
- Mouse model was deemed inappropriate and feasibility and significance was in question. The mouse myocardial infarction model is not appropriate for functional evaluation of human heart tissues.
- There is a weak rationale, particularly with regards to the use of two types of cells using technology that have been tried previously in many labs.
- The team lacks significant expertise in the area.
- It is not clear if the immature cardiac cells will integrate into the tissue.
- It is not clear why the long term stretching is necessary.

Additional Comments

- This area has been studied and published on before. Not clear what the main advantages are.
- Does not differ sufficiently from current approaches to be likely to open new paths forward.

Public Summary for DISC2-09095

Application #	DISC2-09095
Title (as written by the applicant)	A human platform to model microcephaly caused by the Zika virus
Research Objective (as written by the applicant)	We propose to create a human stem cell based platform to determine the impact of the Zika virus during human neurodevelopment.
Impact (as written by the applicant)	A platform to test drugs to neutralize the effect of the Zika virus in human brain cells.
Major Proposed Activities (as written by the applicant)	• To determine the molecular and cellular alterations caused by the Zika virus in the human developing brain. • To determine the molecular and cellular alterations caused by the Zika virus in developed human brain cells. • To determine the mechanism of action of the Zika virus during embryonic formation and explore therapeutic opportunities.
Statement of Benefit to California (as written by the applicant)	The recent outbreak of Zika virus in Brazil prompted the WHO to declare a public health emergency of international concern due to the link between infected pregnant women and microcephalic babies. It is unclear if the virus can also cause neural problems in adults. The virus is spreading quickly and cases of Zika was already reported in California. This proposal will generate a platform to screen potential therapeutic drugs to neutralize the virus deleterious consequences in human brain cells.
Funds Requested	$1,039,760
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 77

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	75
Standard Deviation	6
Highest	85
Lowest	65
Count	15
Number of reviewers who scored 85-100	3
Number of reviewers who scored 1-84	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	9	5	1
Is the rationale sound?	1	8	6
Is the proposal well planned and designed?	4	8	3
Is the proposal feasible?	4	4	7

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The main goal of this application is to develop a human platform to model microcephaly caused by the Brazilian Zika virus. This is a clear and recently emerged medical need. The proposal has a number of clear aims using NPCs, astrocytes and organoids to determine the cellular and molecular effects of Zika virus infection.
- This is an important problem with urgent unmet need.
- Little is known about the cellular impact of Zika virus to the embryo, and thus, this work is important to define the pathology on a cellular level.
- The team has all the necessary resources, and importantly, the team has access to Zika virus isolates
- The project is well designed and logical. However, the three aims are extremely broad, and accomplishing them in the proposed timeline is unrealistic.

Concerns

- There is an enormous need for a better understanding Zika, but what is needed is means of preventing the damage caused by the virus - not the basically descriptive studies that are offered this application.
- The applicant proposes that a human neural progenitor cell system will provide a screening platform for therapeutic compounds. However, it is not clearly specified what compounds would be considered and whether such compounds are meant to address microcephaly or later possible effects.
- Using neural stem cells as the screening platform is a reasonable approach, but the read out in this case is cell death. Cell death inhibitors have already been identified but they are unlikely to be used as a therapeutic.
- The long term goal of the work is unclear. Prevention? Therapy for microcephaly? Long term consequences of infection? Prevention of microcephaly along with identifying long term sequel is perhaps the most urgent need. It is not clear how the application as is stands will impact patients or will inform preventative measures.
- Although the finding of Zika infecting astrocytes would be interesting, it is ultimately not directly relevant to microcephaly observed in infected patients.
- There are concerns regarding the path to translation and whether the questions, while interesting, are focused on the wrong aspect of the problem given that it studies late effects.

Additional Comments

- The applicant might discover novel as of yet identified neuronal defects that are associated with Zika infection. Targeting the rescue or prevention of such defects could be highly relevant for the long-term management of Zika infections that do not present microcephaly. Such experiments, however, are not proposed.
- The suggestion that microcephaly is a distinct feature of the recent Zika Asian lineage viruses that is spreading in South and Central America is potentially relevant although controversial and might inform vaccination strategies. This point should have been better developed.
- Several groups around the world have already published on the mechanism of Zika mediated death in NSCs/organoids, notwithstanding that they were using the African strain. This is not a novel idea (Garcez et al. 2016; Qian et al., 2016; Dang et al.,2016).

Public Summary for DISC2-09098

Application #	DISC2-09098
Title (as written by the applicant)	Use of Human iPSC-derived Endothelial Cells for Calcific Aortic Valve Disease Therapeutics
Research Objective (as written by the applicant)	To develop drugs to treat Calcific Aortic Valve Disease (CAVD), the third leading cause of adult heart disease, by screening a stem cell-based platform based on CAVD patient-derived stem cells.
Impact (as written by the applicant)	CAVD represents a major unmet medical need, with no treatments other than valve replacement. We will identify drugs, already proven to be safe, that normalize gene dysregulation and prevent CAVD.
Major Proposed Activities (as written by the applicant)	• Generate iPSCs from 100 subjects with early onset CAVD and BAV. • Perform genetic analyses of the 100 subjects for enrichment of variants in N1-related gene networks and osteogenic networks. • Derive endothelial cells from CAVD iPSC lines, and study their gene expression under biophysical conditions related to valve calcification. • Screen nine drugs validated in N1+/– iPSC-ECs for their effects on correcting gene network dysfunction in sporadic CAVD patient-derived iPSC-ECs. • Determine efficacy of nine drugs validated in N1+/– iPSC-ECs in preventing CAVD in a mouse model. • Initiate studies of optimal dosing and timing of potential therapeutic compound, which will be determined by best efficacy in Activity 5.
Statement of Benefit to California (as written by the applicant)	This research will benefit California by developing drugs to treat Calcific Aortic Valve Disease (CAVD), a major unmet medical need that imposes a serious economic burden. The only clinical option is valve replacement, with 100,000 patients receiving transplants per year in the US. To address this, we will use a stem cell-based platform based on CAVD patient-derived stem cells to test drugs, already proven to be safe, that normalize gene dysregulation and prevent CAVD.
Funds Requested	$2,400,048
GWG Recommendation	***Recommended for funding, if funds are available.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 94

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	95
Standard Deviation	3
Highest	95
Lowest	85
Count	13
Number of reviewers who scored 85-100	13
Number of reviewers who scored 1-84	0

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	11	0	2
Is the rationale sound?	11	0	2
Is the proposal well planned and designed?	12	0	1
Is the proposal feasible?	11	0	2

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The concept of a clinical trial in a dish for potential small molecule therapeutics for Calcific Aortic Valve Disease (CAVD) is novel and compelling. The project is streamlined with a high translational potential.
- The informatics-based approach to correct aberrant signaling is clever and promising.
- This is a strong application for a well-established investigator aiming to develop a novel medical therapy for patients with aortic stenosis.
- The proposal is novel and the rationale is sound and the studies are feasible and within the expertise of the team.
- The preliminary data are strong and show proof of concept that the small molecule screen can at least partially reverse the genetic profile of iPSC-derived endothelial cells from patients with aortic stenosis.
- If successful, this application could potentially result in the first medical therapy for an otherwise devastating surgical disease.
- This is an untouched area of research - aortic valve disease. There are many patient-specific defects, and a medical alternative to metal valve replacements would be a tremendous advance.

Concerns

- Innovative proposal. Some skepticism about the underlying genetic rationale used in the drug-development process.

Additional Comments

- The proposal could directly yield candidate drugs to treat CAVD.
- The team has identified nine drugs that alter genes in the two identified nodes.
- The team will establish 100 CAVD patient–derived iPSC lines for use in drug screening and will determine gene expression changes in this population of cells.

Public Summary for DISC2-09100

Application #	DISC2-09100
Title (as written by the applicant)	Efficacy of Personalized Exosomes from iPSC-derived Cardiomyocytes for Heart Failure
Research Objective (as written by the applicant)	This proposal will facilitate the clinical implementation of patient-specific iPSC products by validating the efficacy of autologous cell-free exosome therapy.
Impact (as written by the applicant)	Five-year survival of heart failure is a dismal 50%. It is the top diagnosis of hospital admission. Exosomes offer a feasible and effective cell-free approach by simulating endogenous repair.
Major Proposed Activities (as written by the applicant)	• The exosomes from the injury and non-injury models of human iCMs are generated, quantified, isolated, and analyzed for their miRNA content. • Autologous exosomes and their miRNAs derived from the injured iCMs are re-administered to the iCMs to assess the efficacy of activating endogenous self-repair and clarify the mechanism of action. • Changes in the molecular, cellular and functional property of the injured iCMs are measured after the re-administration of the exosomes and miRNAs to determine the in vitro restorative effects. • Genetic changes in fibrosis, inflammation, remodeling, and apoptosis are measured by microarray, reduced cell injury through flow cytometry, and increased contractility via atomic force microscopy. • Electrical activity is measured via patch clamp to quantitate the direct effects of the exosomes on iCMs. • Functional benefit of the exosomes and their corresponding miRNAs is assessed following direct injection into the injured murine and porcine myocardium, using advanced MRI and molecular assays.
Statement of Benefit to California (as written by the applicant)	Five-year survival of heart failure (HF) is a dismal 50% and a leading diagnosis of hospital admission in California. Autologous exosomes offer an alternative approach by simulating endogenous repair of the injured heart. This study allows systematic analysis of the feasibility of cell-free therapy using patient- and injury-specific iPSC-derivatives. The exosomes will circumvent some of the major challenges of stem cell therapy and provide an equally effective therapy for all patients.
Funds Requested	$2,210,438
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 72

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	70
Standard Deviation	4
Highest	80
Lowest	65
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	6	0	9
Is the rationale sound?	0	7	8
Is the proposal well planned and designed?	2	5	8
Is the proposal feasible?	3	4	8

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The mouse experiments are excellent with positive and negative results, but baseline scans to confirm equal groups is important.
- The use of exosomes as a therapeutic agent is timely and justified. The study of exosomes is a very interesting and novel area. The rationale that exosomes could be cardioprotective was established.
- The effect of delivery of signals through the exosomes from cardiac cells appears important.
- Hypoxia angle is interesting.
- It is likely that exosomes and active molecules within exosomes (miRNA, mRNA, proteins ets.) can only be maintained transiently and degrades quickly after release from the host cells. The proposal does address this critical issue. One of the controls for the exosome injections should include transplantation of live iCMs
- It is likely that exosome-based signaling and repair of the injured cardiomyocytes is critical component of the “paracrine therapeutic effect” of stem cell transplantation.

Concerns

- The timing of dosing and dosing from cell to mouse to swine are not adequately explained.
- There is insufficient justification why human iPSCs are used since exosomes are not likely be immunogenic. Human ESCs are likely better source of cardiac myocytes and exosomes.
- How autologous cells would be used to treat the ischemic heart in the acute setting was not adequately explained and did not seem plausible.
- There is insufficient justification for using SCID mice and immunosuppression in pigs. Should exosomes incite immune reaction?

Additional Comments

- Additional safety studies could be done in the pig model. Earlier guidance from the FDA should be acquired.
- Personalized exosomes seem an implausible therapy for acute cardiac events.
- Not a good transition from one aim to the next.
- This is a novel and potentially important application. The lack of distinction between regeneration and salvage is an issue. In particular, the timeframe when the exosomes will be delivered and how they may influence remodeling should be revised.

Public Summary for DISC2-09115

Application #	DISC2-09115
Title (as written by the applicant)	Using human embryonic stem cells to develop novel approaches against neurodegenerative disease
Research Objective (as written by the applicant)	Develop stem cell models of neuronal protein aggregation that enable identification of small molecule activators of protein quality control as treatment option in neurodegenerative diseases.
Impact (as written by the applicant)	We will deliver first-in-class compounds for the development of therapeutic agents against a broad spectrum of currently untreatable neurodegenerative diseases.
Major Proposed Activities (as written by the applicant)	• Identify essential enzymes that mediate protein quality control in human embryonic stem cells and hESC-derived neurons. • Genetic activation of neuronal quality control pathways to counteract neurotoxic protein aggregation. • Develop a screening platform and execute integrated screening campaigns to isolate small molecule activators of neuronal protein quality control.
Statement of Benefit to California (as written by the applicant)	Neurodegenerative diseases affect a growing number of patients in California and beyond. Currently, there is not a single treatment option that slows, halts, or reverse the progression of these deadly diseases. California has invested heavily in centers that investigate the molecular mechanisms of neurodegeneration. The proposed work will extend this investment to push forward first-in-class compounds as therapeutic options against neurodegenerative diseases.
Funds Requested	$1,171,980
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	60
Standard Deviation	0
Highest	60
Lowest	60
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	4	5	5
Is the rationale sound?	2	6	6
Is the proposal well planned and designed?	0	9	5
Is the proposal feasible?	0	8	6

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The rationale for the need to study ubiquitin quality control pathways responsible for protein aggregates observed is sound.
- The combination of genetics and small-molecule screening is powerful but perhaps overambitious for this RFA.
- The strong Principal Investigator (PI) is likely to lead team to some success.

Concerns

- The main postulate of Aim 1 (profiling ubiquitylation enzymes counteracting protein aggregation in ESC vs. ESC-differentiated neurons will identify therapeutic targets) is less convincing.
- There is no mention in the proposal of whether the neurons differentiated from hESCs in culture will be aged artificially. This is an unresolved issue in the field, but an important one given that many neurodegenerative diseases affect neurons that are >50-75 years old.
- There is insufficient preliminary data.
- The timeline is extremely ambitious and accomplishing the three aims will likely take much longer than two years.
- Some technical problems include immature neurons to study disease of aged, which is considered a major flaw

Additional Comments

- It would make more sense to profile ESC-derived neurons against iPSC-derived neurons from patients with neurodegenerative disease (particularly with genetic forms of Parkinson, ALS, or Huntington).
- The aims of this grant are exploratory. This system is overly speculative for a Quest award. More basic science needs to be done before one could evaluate whether or not there is any clinical potential here.
- Most of the preliminary data are on cancer cells rather than targets of this proposal.

Public Summary for DISC2-09123

Application #	DISC2-09123
Title (as written by the applicant)	Immunotherapy for HIV infection using engineered hematopoietic stem/progenitor cells
Research Objective (as written by the applicant)	The therapeutic candidate proposed here is hematopoietic stem/progenitor cells engineered to encode for HIV-specific T cell receptors.
Impact (as written by the applicant)	The success of the proposed studies will test the efficacy of an approach to provide long-lasting functional cure for HIV infection, obviating the need for anti-retroviral therapy.
Major Proposed Activities (as written by the applicant)	• Test if engineered hematopoietic stem/progenitor cells can engraft in humanized mice and differentiate into engineered HIV-specific cytotoxic T cells. • Test if cytotoxic T cells differentiating from engineered hematopoietic stem/progenitor cells are functionally active *in vitro*. • Test if engineered hematopoietic stem/progenitor cells can suppress HIV infection in engrafted mice.
Statement of Benefit to California (as written by the applicant)	HIV affects >200,000 individuals in the State of California. The current anti-HIV treatment needs to be taken constantly for the patient's life time, is expensive, and has negative side effects. The proposed research can address these issues by using engineered hematopoietic stem cells to treat HIV infection. Success of this approach will lead to clinical trials that will be initiated in California and will lead to therapies that will benefit millions of HIV patients in California and worldwide.
Funds Requested	$1,586,934
GWG Recommendation	***Recommended for funding, if funds are available.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 85

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	85
Standard Deviation	8
Highest	95
Lowest	70
Count	15
Number of reviewers who scored 85-100	9
Number of reviewers who scored 1-84	6

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	0	5
Is the rationale sound?	6	2	7
Is the proposal well planned and designed?	8	1	6
Is the proposal feasible?	4	1	10

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The current proposal intends to develop a candidate immunotherapy by engineering Hematopoietic Stem Progenitor cells to encode for HIV specific T cell receptors. The strength of this proposal is the overall design, preliminary data and strength of investigators.
- The research plan is sound and should lead to interesting findings. It is a rational approach to HIV treatment especially if combined with CD4+ cell protection.
- The proposal is based upon significant findings that a rare group of individuals known as “Elite Controllers” carry natural immunologic control over HIV infection. The proposal presents solid preliminary data demonstrating that the PI has identified two TCRs (EC27 and EC5.5) that showed functional activity against HIV.
- There is a high likelihood that successful completion of the proposed studies will address critical issues in HIV pathology and development of HSPC-based immunotherapy.
- There is good rationale for developing a HSPC immunotherapy using TCRs identified from elite controllers. Data from the KK10 peptide pulsed target cells using the EC27 and EC5.5 TCRs are particularly convincing. The in vivo animal data is also encouraging.
- Potential pitfalls and alternatives are discussed.
- The accomplished investigator and team bode well for success of current project.

Concerns

- The overall research plan is sound and should lead to interesting findings. However, the plan does not discuss the constructs in detail and did not discuss how they will restrict expression of the TCR to lymphocytes after HSPC transduction. Expression of the TCR in non-lymphoid cells may be a safety concern.
- The rapid and high mutation of HIV is not taken into account. Long-term control is unlikely based on this mutation rate.
- The proposal presumes that anti-KK10 immunity is the defining characteristic of elite controllers. However, this is an association. Demonstration that reactivity against KK10 does not exist outside elite controllers would be helpful.
- There is a high dependence of Aims 2 and 3 on the success and feasibility of Aim 1.
- The animal model testing appears to have some pitfalls but the investigators have identified them and have alternative approaches.

Additional Comments

- The proposal is risky because the mechanisms operating in elite controllers of HIV are not well understood. However, the basic idea of attempting to mimic the immunological basis of successful control is worth pursuing.
- The approach is somewhat novel in HIV control although several other cell-based therapies also exist.
- A TCR approach is HLA restrictive and therefore a therapy will have to be developed for each HLA type. This is cumbersome, but doable.

Public Summary for DISC2-09140

Application #	DISC2-09140
Title (as written by the applicant)	Ex vivo and in vivo genome editing of hematopoietic stem cells to cure sickle cell disease
Research Objective (as written by the applicant)	A safe and effective gene-replacement technology for repairing of the genetic defect causing sickle cell disease in stem cells of the blood system.
Impact (as written by the applicant)	Our technology has the unique ability to safely and effectively repair the mutation that causes sickle cell disease in patient hematopoietic stem cells both ex vivo and in vivo.
Major Proposed Activities (as written by the applicant)	• Generation of HITI genome-editing vectors that accurately and efficiently correct the HBB locus in iPSCs derived from a patient with SCD. • Optimization of SCD HITI vectors for efficient delivery to HSCs. • Evaluation of SCD HITI vectors in cord blood hematopoietic stem and progenitor cells (HSPCs). • Analyze HITI-mediated targeted knock-in efficiency in long-term repopulating HSCs, and demonstrate functional correction of RBCs in patient cord blood. • In vivo correction of SCD in a humanized mouse model.
Statement of Benefit to California (as written by the applicant)	Blood disorders affect millions of Californians, causing an incalculable personal and economic toll. One benefit that will be derived from this research is a possible cure to some debilitating blood disorders. Another is the training of new scientists to serve as educators and researchers in California. Finally, the discoveries derived from this proposal may lead to new areas of intellectual property that can create high quality jobs in biotechnology and pharmaceutical industries in California.
Funds Requested	$2,676,240
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 74

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	75
Standard Deviation	7
Highest	90
Lowest	60
Count	14
Number of reviewers who scored 85-100	2
Number of reviewers who scored 1-84	12

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	10	2	2
Is the rationale sound?	5	1	8
Is the proposal well planned and designed?	4	3	7
Is the proposal feasible?	1	7	6

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The use of genome editing is interesting. This a novel method that may allow *in situ* gene editing, and may have considerable generality for carrying out gene therapy on stem cells.
- The application and proposed method are a very exciting.
- The principal investigator is a world class researcher.
- The team is very strong.
- Potential impact of this proposal is high as genome editing of blood disease seems very tractable.

Concerns

- The lack of preliminary data in a relevant cell model is a significant issue with this application. This issue raised concerns about feasibility and significantly reduced enthusiasm among reviewers.
- It is unclear why Aim 1 uses iPSC and Aim 2 cord blood since the goal is to correct hematopoietic stem cells.
- The goal of Aim 1 appears to be to identify the best targeting vector to induce breaks. However, the cells, environment and vectors (adeno) used in Aim 2 are all different than in Aim 2. It is not clear how the results in Aim 1 will translate to the developing efficient targeting in Aim 2.
- The hypothesis is not clearly supported; there is a lack of sufficient preliminary data that are relevant for the problem that is proposed.

Additional Comments

- The preliminary data are generated with a different cell type and different gene.
- It is unclear how important Aim 1 is since it concentrates on cell lines and not stem cells. Success in targeting a locus in cell lines may not mean that the same approach will work with adeno vectors in ESCs *in vivo*.
- There are no data on editing the gene that they are proposing to alter. The team needs to test the gene of interest.

Public Summary for DISC2-09150

Application #	DISC2-09150
Title (as written by the applicant)	IPSC-Based Diagnostic Platform for Neurogenetic Disorders using an RNAseq Approach
Research Objective (as written by the applicant)	We will utilize cells that we deposited to CIRM from which IPSCs were generated to advance diagnosis of autism, epilepsy and cerebral palsy conditions.
Impact (as written by the applicant)	We think the results will impact the way doctors make diagnosis in the future, by incorporating IPSC-based modeling into their workflow, and to increase yield of genetic testing.
Major Proposed Activities (as written by the applicant)	• Obtain from CIRM the cell lines we deposited, check their quality, and collect their genetic material. • Similar to Activity 1, collect genetic material from the original skin cells we collected from these patients. • Optimize methods to turn IPSCs into neural cells using chemicals rather than expensive and time consuming standard methods. This will allow us to obtain genetic material from patient neural cells. • From the neural cells from Activity 3, collect genetic material. Profile the genetic material by examining the RNA from the 3 cell types from each patient and compare results. • Compare the result from Activity 4 with data already on-hand from these patients, in order to find causes of disease in patients that would not be possible without their stem cells. • Try to expand this method to develop business ventures across different classes of disease.
Statement of Benefit to California (as written by the applicant)	California leads the world in stem cell biology, but for neurological disease, implanting stem cells is not feasible or rationale in most cases. In order for stem cells to impact neurological disease, we need to develop better cellular models and be able to understand the impact of genetic mutation on patient cells, especially their neurons. We hope that our research leads to improved diagnostic yield of recent gene testing approaches, and changes in the way doctors diagnose and treat disease.
Funds Requested	$1,083,600
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: 65

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	65
Standard Deviation	2
Highest	70
Lowest	60
Count	15
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	15

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	2	6	7
Is the rationale sound?	3	4	8
Is the proposal well planned and designed?	2	4	9
Is the proposal feasible?	2	8	5

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposed approach may aid in the identification of the genetic pathways underlying neurodevelopmental disorders.
- The proposal will utilize RNAseq and miRNAseq from patient/family iPSC derived NPCs in addition to classical whole genome sequencing to uncover new disease mechanisms and disease genes. This methodology may be used towards a generalizable platform for iPSC-based genetic diagnosis of human disease.
- Exome capture and RNA seq appealing approach likely to produce much data.
- The Principal Investigator (PI) is excellent.

Concerns

- It is known that reprogramming introduces many de novo mutations, which can confound the identification of any causative mutation. Using more than one clone of iPSC will help identifying driving mutations. However, this would duplicate the workload, making it even more unrealistic.
- The candidate technology does not directly facilitate the discovery, development or use of stem cell-based therapies.
- Very few potential pitfalls and alternatives are acknowledged.
- The feasibility of deriving and differentiating large number (500+) of patient iPSCs could be problematic, given that the PI does not have solid expertise in these techniques.
- This is a very ambitious project and unlikely to succeed. The approach of using RNA Seq may add additional details in terms of mutations but will continue to miss many. The approach also requires expression and the select number of stem and progenitor states that will be profiled may significantly limit the insights.
- There is a huge amount of work and no clear idea of what the final product will be for translation. For example, the cell lines are not yet generated, and there is doubt that this work can be completed in time.

Additional Comments

- There is a high dependence of aims on the success and feasibility of previous aims.
- The team may want to increase the staffing for the stem cell culture, given the workload proposed.
- Data collection plan needs more structure. It comes across as too much of a “fishing expedition”.

Public Summary for DISC2-09152

Application #	DISC2-09152
Title (as written by the applicant)	Development of Neuronal Autophagy Inducers (NAI) to Treat Huntington's Disease
Research Objective (as written by the applicant)	To identify a small molecule drug that safely and potently blocks degeneration of human iPSC derived neurons from multiple patients with Huntington's Disease (HD) and shows activity in vivo in mice.
Impact (as written by the applicant)	Patients with the neurodegenerative disease Huntington's disease would benefit. Other neurodegenerative disease patients like ALS, Parkinson's and Alzheimer's disease could also benefit.
Major Proposed Activities (as written by the applicant)	• Test 40 NAIs for efficacy in reducing degeneration of human i-neurons derived from six different HD patients with varying CAG repeats and induction of autophagy in those neurons monitored by RM. • Test those NAI effective in reducing degeneration of HD i-neurons in dose-response studies to determine their neuroprotective potency and optimal dose in autophagy induction. • Using RM, test NAIs for safety and lack of detrimental effects on survival of human control i-neurons derived from healthy volunteers. • Using mass spectrometry, identify secreted molecules whose levels are modulated by autophagy induction in vitro in human i-neurons from patients and healthy volunteers. • Develop immunoassay for secreted mutant HTT modulated by autophagy induction in human i-neurons. • Evaluate the modulation of target engagement biomarker candidate in response to drug treatment in vivo in mice.
Statement of Benefit to California (as written by the applicant)	Neurodegenerative diseases are devastating for patients, their families, and society and the problem will grow as our population ages in California, the US and the world in general. No therapeutic is available to slow the progression of any neurodegenerative disease. In this proposal, we focus on Huntington's disease but our study will benefit tens of thousands of California patients with other neurodegenerative diseases, including ALS, Alzheimer's and Parkinson's disease.
Funds Requested	$1,369,987
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	8	5	1
Is the rationale sound?	3	10	1
Is the proposal well planned and designed?	6	6	2
Is the proposal feasible?	1	10	3

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- This proposal contains high-impact research with a novel hypothesis that autophagy inducers may effectively treat Huntington's disease, with interesting patient-derived models.
- The aims are feasible and within abilities of team.
- Concerns were raised at review about completeness of preliminary data and thus, it was difficult to evaluate. The approach seems sufficiently promising that it should not be abandoned on the basis of one negative result.

Concerns

- While there is much to like in this application, and initially there was considerable enthusiasm, the failure to disclose the lack of success in previously funded and very similar studies make it impossible to evaluate this application.
- The applicants failed to incorporate critical data from their progress report in this application. Briefly, the applicants conducted preliminary experiments in Hti neurons with their lead compound and reported in their progress report that these compounds did not affect survival of Ht i neurons. These data are thus not supporting the overall hypothesis and should have been discussed.
- It is not clear if the system will work in humans.

Additional Comments

- Previous studies on ALS and cell death made the prediction that studies in mouse cells would reveal principles that applied to human cells. Testing of this prediction demonstrated the hypothesis was wrong, as presented in previous progress reports. The previous failure mandates discussion of this failure and discussion of reasons why this difficulty has now been overcome.
- Reviewers noted that the application was not transparent about reporting results (negative) from the progress report.

Public Summary for DISC2-09154

Application #	DISC2-09154
Title (as written by the applicant)	Developing a stem cell-enabled peripheral blood-based diagnostic for bipolar disorder based on the lithium response pathway
Research Objective (as written by the applicant)	Validate a diagnostic assay derived from accessible peripheral blood to predict a process ongoing in the inaccessible CNS that is relevant to the cause & novel treatment of psychiatric disorders.
Impact (as written by the applicant)	1) Psychiatry & neural dysfunctions; 2) Use of stem cells to molecularly model polygenic complex disorders with unknown underlying pathological genes, proteins, & pathways beyond simply phenotype.
Major Proposed Activities (as written by the applicant)	• Generation, characterization, & neuronal differentiation of a sufficient range & number of peripheral blood-derived hiPSCs & hNPCs. • Neurite outgrowth assays in relation to CRMP2 ratios. • Neurite proteomics in relation to CRMP2 ratios. • Dendrite spine morphology & function in relation to CRMP2 ratios. • Neuronal function assays via calcium imaging & multi-electrode array. • In vivo correlation of CRMP2 ratios with behavior & histology both in mouse models of bipolar disease (& other mutants) as well as well-archived actual bipolar patient brain specimens.
Statement of Benefit to California (as written by the applicant)	We propose to develop an assay based on cells that, though obtained from the peripheral blood of a patient, can be manipulated to provide information on likely brain circuitry & may help in the diagnosis of & drug selection for that patient. The assay is designed for bipolar disorder (a common & lethal disease), but may be applicable to other neurological conditions. The assay may help develop better psychiatric drugs based on the mechanisms causing the disease.
Funds Requested	$1,035,720
GWG Recommendation	***Not recommended for funding.***
CIRM Team Recommendation	***CIRM Team concurs with the GWG's recommendation.***

Scoring Data

Final Score: Below 60

Up to 15 scientific members of the GWG score each application. The final score for an application is the average of the individual member scores. Additional parameters related to the score are shown below. A score of 85-100 indicates that an application is “recommended for funding” and a score of 1-84 indicates that an application is “not recommended for funding.”

Median	---
Standard Deviation	---
Highest	---
Lowest	---
Count	14
Number of reviewers who scored 85-100	0
Number of reviewers who scored 1-84	14

Score Influences

Proposals were evaluated and scored based on the criteria shown below, which are also described in the RFA. The scientific members of the GWG were asked to indicate how their evaluation of the proposal against each criterion influenced their overall score. The total number of reviewers indicating a positive, negative, or neutral influence for each criterion is shown.

Criterion	Positive Influence	Negative Influence	Neutral Influence
Does the proposal have a potential for impact?	5	7	2
Is the rationale sound?	0	9	5
Is the proposal well planned and designed?	1	8	5
Is the proposal feasible?	6	6	2

Reviewer Comments

The following is a compilation of comments provided by multiple reviewers following the panel's discussion and scoring of the application. All reviewers were asked to provide brief bullets on key strengths, concerns, or recommendations related to the proposal that CIRM compiled and edited for clarity.

Strengths

- The proposal seeks to develop a specific biomarker for bipolar disorder treatment response, which if successful would significantly advance current psychiatric therapeutics. Even if not specific for bipolar disorder (BPD), the model could potentially help predict specific kinds of drug response.
- The public health importance of BPD diagnostics and therapies is off the charts. Diagnostic blood test for BP could be useful.
- Great preliminary data are present with a caveat. The authors apparently believe that a single protein is important and they do not discuss or mention the other mechanisms. However, they do a really good job of analyzing this particular protein pathway.

Concerns

- The main problem is that the proposal hinges entirely on preliminary data that need validation. Only following validation would it make sense to do studies of the type proposed.
- From the data presented it is not clear:
  - whether the neurons were generated from peripheral blood.
  - how consistent and pure the cultures are.
  - what pitfalls are likely to be encountered.
- All subsequent milestones depend on the success of milestone 1. It is not clear why the applicant is not proposing a drug screen on fibroblasts derived neurons as an alternative to the diagnostic approach.
- According to the data provided by the applicant, lithium can inactivate GSK3b directly and thus affect downstream targets. Based on this broad action, it is likely that lithium affects other brain cells that can have an indirect effect on the neuronal population. This aspect is not considered.
- There is lack of context in the proposal. It is too focused on the idea that there is only one mechanism of action of lithium. They need to show awareness of other potential lithium actions.
- The application focuses on one hypothesis and ignores others; application ignores or dismisses other relevant studies.
- There is some nice preliminary data showing some effects of lithium on bipolar cells. However, the authors seem to claim that what they observe is the ""lithium response pathway". They don't seem to have eliminated all other possible actions of lithium.
- Most genetic BPD efforts are finding genes in several other pathways (e.g., synaptic transmission) - they quote articles from 2009 rather than more recent work. The claims about CRMP2 are unpublished and unreviewed. The cited references (3-10) are stale and don't directly support the claim. There is a lot of preliminary data presented. It might be a stronger proposal to validate the preliminary data, rather than to assume it as a 100%-true fact, and immediately use it as a foundation for diagnostics.
- The project might require a larger budget. A little more in-depth budget justification would help clarify the budgetary feasibility. Nine milestones over 24 months - may be too aggressive.
- There is a claim that the preliminary data will be published soon. But they were presented at a conference in 2014. If the preliminary data is that strong, and is a high priority, high impact result, why is it not published yet?

- In the age of systems biology, a biomarker revolving around a single phosphorlyated protein seems almost passé. It is not going to have the sensitivity, specificity of a test based on multiple markers.

Additional Comments

- It is highlighted that the iPSC approach could be used for drug screening to define more favorable drugs and lithium and perhaps to identify new drugs for non-responders. This is however not the goal of this application.
- As acknowledged by the applicant, it is unclear whether the molecular target represents a response to lithium in the LiR BPD or represents an endogenous change in set point of p-CRMP2 in a subpopulation of BPD that will ultimately respond to Li.
- It is likely that the range of p-CRMP2/t-CRMP2 varies in non-affected people. As all data are pooled values, it is not clear how robust the change in the ratio is in the target population. Aa single patient outside the context of a large parallel run control cohort.
- The extent of the IRB approval is not clear. Can patients' lines only be used for the outlined milestone?
- "Blunting phosphorylation of CMRP2 at the motif modified by Li appears to be therapeutic in mouse models of LiR BPD." There are no good animal models of bipolar.
- A paper last year out of Rusty Gage's lab at the Salk showing bipolar IPS cells show a hyperexcitable phenotype. It may hint at an alternate mode of action or perhaps if argued correctly support the applicant's proposal. They dismiss that work as "phenotyping and phenomenology." Rather than dismiss this other important observation, they should integrate it.
- Reviewers suggested that an examination of all of the various mechanisms of action that are considered with scientific support in this review article (for example - other reviews provide similar summaries): CNS Drugs (2013) 27:135–153 Potential Mechanisms of Action of Lithium in Bipolar Disorder Mali et al.
- In particular, several molecular mechanisms other than along the GSK-3 pathway should be considered: Lithium "primarily interferes with the binding of [Mg] at specific metal ion binding sites and disrupts the function of a number of essential proteins. For example, lithium inhibits inositol monophosphatase (IMPase), glycogen synthase kinase 3 (GSK-3), and phosphoglucomutase (FGM). etc.